A POPULATION STUDY OF LOW BIRTH WEIGHT INFANTS WITH SPECIAL REFERENCE TO IMPAIRED FETAL GROWTH

by John Ives Cater

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University of Edinburgh.

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To Bel, Jenny, Alison and Ilona for their patience

CONTENTS

ABSTRACT

The major aims of this project were, first, to study a cohort of low birth weight infants and their carefully matched controls in order to determine the effects of perinatal disease and social circumstances on subsequent long term performance; and, second, to improve the current definitions of intrauterine growth retardation. The potential contribution to knowledge of this work lies in its prospective design using a clearly defined catchment area and carefully matched individual controls. As a consequence it has been possible to demonstrate significant differences between the maternal backgrounds of low birth weight and control infants and to conclude that low birth weight infants are in the main derived from biological backgrounds inferior to those of their matched controls.

My major interest during the study was to improve the definition of intrauterine growth retardation. Analysis of eight different methods presented in Chapter V highlights the difficulties of achieving such an objective. The difficulties arise because of the multiplicity and variety of biological factors which influence fetal growth; these are discussed in the chapters dealing with maternal contribution to fetal growth, outcome of sibling of LBW infant, congenital abnormalities and the corroboration of the last menstrual period by the total maturity score.

As a background to the study, the relevant literature is reviewed, and a detailed discussion is presented of the methodological problems encountered in the setting up of a low birth weight study. One section describes several new clinical features related to gestation or fetal growth. Further details are given in a chapter describing a number of neonatal measurements, such as the Apgar

score and biochemical data. Lastly, there is a section describing the morbidity pattern in the cohort during infancy and early childhood.

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PREFACE

During the last fifty years a great deal has been written about the problems of infants of low weight at birth. Despite this voluminous literature, it is still not clear which are the most important factors adversely affecting the long-term development of these babies. It is the purpose of this thesis to present the results of a study of low birth weight (LBW) which was designed to examine the effect of a number of variables on the infant's condition at birth which might influence subsequent progress and ultimate outcome. It was also hoped to define and classify more precisely the population of infants grouped under the general term "low birth weight".

CHAPTER I

THE CHANGING PATTERN OF CARE OF THE NEWBORN INFANT

In this century there has been progressive decline in the neonatal mortality rate in the United Kingdom. More recently there has been a fall in the mortality rate of infants weighing less than 1000 g at birth (Stewart et al, 1977). Such an improvement is hardly surprising in view of the numerous advances that have taken place in neonatal care. However, discretion should be exercised in the use of mortality data as indices of care. Until all births above a given weight and menstrual age (e.g. 400 g and 20 weeks) are included, mortality data will be suspect. Hospitals that act as referral centres may only receive low birth weight infants who are likely to survive, so that their low mortality rates may be misleading.

Controlled trials based on mortality data are notoriously difficult to interpret due to the numerous factors which influence death rates. In the case of the newborn infant, birth weight, menstrual age, race and sex are some of the variables known to affect survival.

Kitchen and Campbell (1971), in a controlled trial of infants whose birth weights were between 1000 - 1500 g, compared parenteral feeding and active management of respiratory distress syndrome (R.D.S.) with routine feeding and management of R.D.S. They failed to show an improvement in mortality rates at the 5% level for parenteral feeding but found that active treatment of R.D.S. with sodium bicarbonate was associated with an increased survival rate. The groups appeared well matched except for a preponderance of males in the intensively treated group. If the increased mortality rate of males had been taken into account the advantages of active treatment might have reached the level of statistical significance.

Buetow and Klein (1964) demonstrated by controlled trial that maintenance of body temperature favoured survival in the newborn infant with birth weight below 1500 g. On the other hand, the work of Bucci et al (1971) typified the problem of a poorly-designed controlled trial. It was hoped that mortality (a complex factor influenced by numerous variables) would discriminate when 3 different hypotheses were tested in a small group of infants. They tested the efficacy of administering three antibiotics routinely as opposed to one, the use of γ globulin, maintenance of pH of the blood and the use of plasma in the prevention of haemorrhage. It would have been more appropriate to try to establish the advantage of prophylactic routine antibiotic therapy against untreated controls. Prophylactic antibiotic therapy in infants of very low birth weight is not widely practised. These authors postulated that infection caused death and hence γ globulin was prescribed. As it is known that γ globulin has no action against bacteria, it would seem that such administration is of dubious benefit. Administration of alkali has been shown to benefit infants with R.D.S. but the indiscriminate elevation of the blood pH to an arbitrary figure may subject the patient to hazards of infection and osmolar overload. Trying to answer three questions utilising mortality as an indicator made it impossible to discern if, for example, triple antibiotic therapy really conferred any advantage. Alden et al (1972) attempted to assess the effects of advances in care of babies with an admission weight of below 1000 g. Their sample was highly selected as 82% of the babies were transferred from outlying hospitals, and it seems probable that only infants likely to survive would have been transferred. Follow-up showed that 9 out of 22 infants were physically normal and 12 out of 22 appeared mentally normal. It was noted that 5 out of 22 had retrolental fibroplasia. The value of such a study is limited in view of the high percentage of babies admitted from outlying hospitals.

Due to the complexity of controlled human trials, animal experiments have often been used. Whilst such studies have made important contributions to the reduction of morbidity and mortality in the neonatal period, it is unwise to assume that the results are always relevant in man. It is proposed to review the existing evidence from controlled clinical trials relating to recent advances in newborn care. Where such data are unavailable, reports of scientific studies in the major areas where improvement has taken place will be considered.

(1) Asphyxia

Asphyxia occurs when respiration fails to start or ceases, with the development of hypoxia and hypercapnia, though the clinical definition is far from precise. McDonald (1967) noted that children with white asphyxia as opposed to blue asphyxia at birth had reduced IQ's later (the clinical diagnosis of white asphyxia indicates a severe degree of shock). The Apgar score now widely used as an indication of the degree of asphyxia demonstrates that infants with scores of 0 - 1 at 1 and 5 minutes after birth have neonatal mortality rates of 23% and 49% respectively (Drage and Berendes, 1966). Results from the American Collaborative Study (Drage et al, 1966) show the 5 minute Apgar score to be the best indicator of neurological abnormality (muscle tone, motor development and prehensile grasp): this conclusion may not be valid because of the range of ages and times of examination (48-60 weeks) and the fact that no allowance was made for the difference in post-conceptual age of pre-term infants. One might have expected low Apgar scores to be more closely related to neurological damage but it must be stressed that the Apgar score only reflects conditions in a short period of time around birth.

There is no shortage of suggested methods for resuscitating the newborn baby, but in secondary apnoea animals can only be effectively resuscitated by ventilation of the lungs (Moore and Davis, 1966). Intravenous (I.V.) sodium bicarbonate may be used to correct severe acidosis which persists despite artificial ventilation (Hull, 1971). I.V. glucose (Mott, 1961) can increase the survival of asphyxiated animals.

Modern resuscitative measures are highly effective in the asphyxiated newborn and have played an important part in the reduction of neonatal morbidity and mortality.

(2) Apnoea

McDonald (1967) noted at follow-up that the mean IQ of children who had experienced neonatal apnoeic or cyanotic attacks was similar to that of those who had not. Apnoea as opposed to a cyanotic attack was not defined in this multi-centre study and the omission reveals one of the fundamental problems in long-term studies of sequelae of hypoxia at birth. Daily, Klaus and Meyer (1969) described the clinical events and defined apnoea as "a non-breathing interval longer than an infant can tolerate without bradycardia and cynanosis. This may be 20 seconds for a larger pre-term infant and for a small one may be as short as 5 seconds." Such a definition separates those pre-term infants displaying irregular respiration due to decreased sensitivity of the respiratory centre to CO_2 (Levine and Gordon, 1942) from those with pathological apnoea. Although apnoea may be secondary to R.D.S., intraventricular haemorrhage, hypoglycaemia, hypocalcaemia and infection, all of which require specific therapy, the use of apnoea alarm mattresses (Blake et al, 1970) should help to reduce the morbidity by drawing immediate attention to potentially damaging apnoea. The use of aminophylline and similar pharmacological agents have proved useful in the management of apnoea (Kuzemko and Paala, 1973).

(3) Antibiotic Therapy

The British Perinatal Mortality Survey (Butler and Bonham, 1963) demonstrated that 13% of early neonatal deaths were due to pneumonia. It would be expected, therefore, that antibiotic therapy would reduce the overall morbidity rate, though against this must be set the fact that serious side-effects have been associated with the administration of sulphonamides and chloramphenicol.

(4) Bilirubin

Though approximately 50% of newborn infants become jaundiced, only a small number develop long-term sequelae. In a study of hyperbilirubinaemia (Indirect-reacting bilirubin >15 mg/ 100 ml) due to haemolytic disease, Hyman et al (1969) found that sensori-neural hearing loss and athetosis were significantly associated with raised bilirubin levels ($\geq$ 20mg/ 100 ml). The results may have been influenced by the use of streptomycin and vitamin K, the latter in high dosage by present standards. It is also difficult to determine the influence of anaemia and the complications of pre-term delivery in the sequelae of rhesus isoimmunisation. Boggs, Hardy and Frazier (1967), in the Collaborative Study, found that increasing neonatal hyperbilirubinaemia was associated with lower mental and motor scores at eight months of age in all birthweight groups. It is not evident whether allowance was made for the reduced post-conceptual age of pre-term infants but this influence should mainly affect the lower birthweight groups. It will be of interest to see if the findings at such an early age are subsequently confirmed. The great diminution in athetoid cerebral palsy testifies to the efficacy of exchange transfusion and with the development of maternal anti-D administration, rhesus isoimmunisation should be virtually abolished.

Less effective methods of reducing hyperbilirubinaemia by phototherapy and phenobarbitone administration have been reported. Lucey, Ferreiro and Hewitt (1968) showed in a controlled trial that phototherapy significantly reduced hyperbilirubinaemia. McMullin, Hayes and Arora (1970) gave phenobarbitone to affected rhesus babies and reduced the number of exchange transfusion required by the treated group.

In the future the dangers of hyperbilirubinaemia should be virtually avoided by anti-D or at least significantly reduced by these advances in treatment.

(5) Blood Pressure

The measurement of blood pressure should be an integral part of intensive care. It has been neglected in the past due to the difficulties of making precise measurements in the newborn infant, but simple and accurate equipment, e.g. the Newcastle Sphygmomanometer (Ashworth, Neligan and Rogers, 1959) is now available. Continuous monitoring during intensive care usually necessitates umbilical artery catheterisation. Hall and Oliver (1971) reported improved survival (5/18) in treated infants with blood pressure less than 40 cm H_2O on admission compared with an untreated control group (0/19). The latter appeared to have a lower mean birth weight and menstrual age, which might have accounted for the difference in survival between the two groups. The findings were statistically significant ($p < 0.05$). Phibbs (1969) reported that hypotension is particularly liable to occur with blood loss, the small premature infant with asphyxia and respiratory distress immediately after birth, and in asphyxiated breech-delivered infants. Whilst the management of hypotension due to blood loss is now established, the rational treatment of asphyxial hypotension remains to be clarified. The detection and management of neonatal hypotension would seem a promising way to further reducing morbidity and mortality.

(6) Intracranial Haemorrhage

Though an important cause of neonatal morbidity and mortality, the aetiology of intracranial haemorrhage remains obscure. The association of subdural haematoma with traumatic delivery is well recognized; the mechanism of subarachnoid and intracerebral haemorrhage is less clearly understood, whilst that of intraventricular haemorrhage remains purely speculative. It is well documented that intraventricular haemorrhage (IVH) is an important cause of perinatal death. Harrison, Heese and Klein (1968) considered that prolonged anoxia was a major factor in intracranial haemorrhage. MacGregor (1960) postulated that poor support of the veins in the proximity of the ventricles was responsible. Towbin (1968) selected illustrative case histories to support his view that circulatory failure was the principal cause: venous infarcts resulted in the vessels of the subependymal layers of the cerebral hemispheres which subsequently ruptured into the ventricles. Gray et al (1968) noted that in low birth weight infants a low thrombotest (less than 10%) was associated with death from intracranial haemorrhage, though a causal relationship was not established. From CSF protein studies, Cole et al (1974) suggested that raised cerebral venous and capillary pressure, occurring as a result of cardiac failure secondary to hypoxia, was responsible by causing rupture of the terminal veins and allowing filtration of plasma protein into the CSF. The role of sodium bicarbonate has been hotly disputed over the last few years and on the balance of evidence seems to be associated with rather than a cause of intraventricular haemorrhage. Hambleton and Wigglesworth (1976) have suggested that in situations of hypoxia and hypercapnia, a rise in arterial pressure may cause rupture of the capillaries in the germinal layer, giving rise to subsequent haemorrhage. From the above discussion it is clear that some advance has been made in understanding the mechanisms of intracranial haemorrhage. Clarification of the aetiology of intraventricular haemorrhage would be a major advance and would enable better management to reduce mortality and long-term sequelae in infants of low birth weight.

(7) Haemorrhagic Disease

The causes of haemorrhage in the newborn can be divided into two categories, of which one - classical haemorrhagic disease - is no longer a problem (Hathaway, 1970) largely due to the administration of prophylactic vitamin K. With greater understanding of clotting mechanisms, it has been possible to identify disseminated intravascular coagulation as the other major patho-physiological mechanism (Hathaway, 1970). Further research in this important area should result in a reduction of both morbidity and mortality.

(8) Viscosity of the Blood

There are numerous anecdotal references in the medical literature to polycythemia causing symptoms in light-for-dates infants, e.g. (Humbert et al, 1969). On the basis of such data it is not possible to isolate the effects of polycythemia from those of other factors associated with impaired fetal growth, e.g. hypoglycaemia, dehydration and hypoxia during delivery. New methods of viscosity measurements suggested (Kontras and Bodenbender, 1968) that packed cell volumes (pcv) above 50-60% were associated with exponetial increases in the viscosity. They also noted that values for viscosity were lower in the aorta and capillaries than in the arterioles. Virtually no comment is made in the literature on this important finding. In in vitro experiments, (Dintenfass, 1963) found that blood remained fluid even if the haematocrit was 100% (comparative studies on a suspension of rigid particles would solidify at volume concentrations below 70%) due to the thixotropy of blood. Red cells undergo reversible sol gel transformations under action of shear.

Kontras (1972) recommends phlebotomy with replacement or modified exchange in symptomatic babies irrespective of aetiology. In some of the published work where symptoms are attributed to polycythemia, no causal relationship has been established and one suspects that polycythemia, being readily measurable, is incriminated without good grounds. Moreover, there is a certain amount of evidence to suggest that in vitro studies may not represent in vivo conditions. A carefully controlled prospective trial would resolve such a question and result in improved management of the newborn.

(9) Hypoglycaemia

Early reports on the association between hypoglycaemia and neonatal convulsions stimulated widespread interest in the subject. Methods of estimating blood glucose were at first inaccurate due to the inclusion of reducing substances. The relatively recent introduction of the glucose oxidase method and specimen preparation (Cornblath and Reisner, 1965) has enabled accurate and reproducible blood glucose results to be obtained. For the purposes of this discussion only values based on the glucose oxidase method will be considered. Attempts to define normal blood glucose levels in the neonate have a long and chequered history. Results were noted to differ between normal and LBW infants. (Baens et al, 1963) studied 109 premature infants weighing between 735-2190 g and 15.3% were observed to have blood glucose levels below 30 mg/100 ml in the first two months of life. Of the LBW group, 6 (1.2%) had a single blood glucose value below 20 mg/100 ml. Hypoglycaemia (Cornblath et al, 1966) in the normal newborn infant is defined as a sequential blood glucose value below

30 mg% during the first 72 hours of life and below 40 mg% thereafter, and under 20 mg in the infant of low birth weight after $3\frac{1}{2}$-$4\frac{1}{2}$ hour test. There is little doubt that hypoglycaemia causes histological change in cerebral tissue. Anderson, Milner and Strich (1967) recorded cellular change at autopsy in untreated hypoglycaemic newborns when compared with a treated hypoglycaemia control group.

Though the present definitions of hypoglycaemia have introduced a degree of standardisation they are unsatisfactory from three aspects. Firstly, they are based upon so-called normal populations in hospital. This takes no account of the fact that such institutions act as referral centres for infants at risk. Secondly, infants who are symptomatic and respond to glucose but have a blood level above the arbitrary value are not included. Finally, the meaning of the word "sequential" is undefined.

Despite the theoretical uncertainties, hypoglycaemia appears to have become less of a problem since the introduction of early feeding. Because glucose can easily be measured under adverse conditions, more has been attributed to low levels of blood glucose than is probably warranted. Further understanding of its metabolism and clinical effects may be expected to lead to improving standards in newborn care.

(10) Intravenous Therapy

The judicious use of intravenous therapy is a valuable aid to management of the ill patient. In the newborn, the challenge of securing and maintaining an adequate venous route other than via the umbilical vessels has been formidable. It is known that "the use of indwelling catheters in the umbilical vessels can lead to improved care of sick newborns" (Kitterman, Phibbs and Tooley, 1970). However it may also lead to serious complications.

The recent development of infusion pumps capable of delivering fluid volumes appropriate to the requirements of the newborn infant enables short term fluid requirements to be met via a peripheral vein. Despite the many problems such as infection, catheter placement and osmolar load, improvements in equipment and technique have now made it possible to supply nutritional support by vein over a long period with subsequent adequate weight gain (Filler et al, 1969).

(11) Nutrition

The process of birth irrevocably interrupts the continuous nutritional supply to the fetus. Despite the fact that, left to themselves, both man and animals suckle shortly after birth, it became fashionable in the late 1940s and 50s to delay feeding for several days. Such a policy was supported by the necropsy findings of Rhaney and MacGregor (1948) who recorded a high incidence of inhalation of vomit - particularly in LBW infants. Death was attributed to inadequacies of nursing care.

During the next twenty years the pendulum has swung back to early feeding. Shelley (1961) showed in animals that liver glycogen falls within two or three hours of birth to 10% of the initial value despite early feeding. Wu et al (1967) noted that blood glucose levels were higher at 24 hours in infants fed early when compared with those fed at later ages. Hubbell et al (1961) demonstrated that infants of diabetic mothers fed at four hours of age had significantly lower serum bilirubin levels than those who started feeding at 48 hours. Smallpeice and Davies (1964) in an uncontrolled trial (a comparison was made between hospitals) demonstrated that early feeding reaching adequate volumes (150 ml by the fourth day) did not increase the mortality rate despite regurgitation of feeds by one third of the infants. Wharton and Bower (1965) noted a considerably higher mortality in infants fed early, but, from their own analysis, statistical significance was not reached at the 5% level. In a carefully controlled study of 90 babies, the early administration of nutrients by vein to babies with birth weight of less than 1500 g has been shown - by mortality rates - to be superior to nasogastric or delayed feeding (Cornblath et al, 1966). With increasing knowledge of the nutritional requirements of the newborn LBW infant, early administration of electrolytes (Babson, 1971) has been recommended. Total nutritional support by intravenous alimentation resulting in adequate weight gain has been reported (Filler et al, 1969), though avoiding the hazards of sepsis, osmolar load and catheter siting necessitates considerable medical expertise.

It would be very important to establish whether different patterns of feeding can affect growth and development but great care should be exercised in relating such results to those found after severe malnutrition. A number of studies have demonstrated impaired intelligence following severe infant and early childhood malnutrition. Hertzig et al (1972), employing sibling control, noted that IQ was significantly lowered in the affected infants. The siblings had performance IQs intermediate between index cases and non-family controls. The authors note that, due to the customs of the society concerned, the biological fathers might have been different for the siblings. The low scores of the unaffected siblings suggested that the environmental background of these families was less than satisfactory, and indeed infants undergoing severe malnutrition are likely to be socially as well as nutritionally severely deprived. In a retrospective analysis Drillien (1964) postulated that delayed start of feeding was responsible for the high rates of handicap in her series. She noted that in the years of particularly high handicap rates, infants took longer to regain their birth weights. On the other hand, excessive nutrition has its dangers. From about the thirtieth week of gestation to approximately the end of the first year of extra-uterine life, adipose tissue responds to excess nutrition by an increased cellular multiplication. Despite the problems of uniform cell sampling, the concept of adipose cell sensitivity (Brook 1972) has furthered our understanding of growth. Careful attention to feeding and the correct time of administration should improve the rate of survival in the newborn period and the quality of survivors.

(12) Idiopathic Respiratory Distress Syndrome

Idiopathic Respiratory Distress Syndrome (RDS) accounted for 15.0 per cent of early neonatal deaths in the British Perinatal Mortality Survey (Butler and Bonham, 1963). The aetiology is still obscure, though many hypotheses have been advanced. Avery and Mead (1959) suggested that lack of surfactant was the cause. Chu et al (1965) postulated that reflex vasoconstriction due to such factors as hypoxia, hypovolaemia, hypothermia and acidaemia caused centralisation of the circulation and the term "pulmonary hypoperfusion syndrome" was coined. There is evidence in support of both these

hypotheses and it seems probable that several factors are involved in the genesis of the syndrome.
The belief that pulmonary vasoconstriction is important gives hope that therapy may influence the clinical course. Usher (1963) advocated IV sodium bicarbonate and glucose. In a further controlled study, early treatment with bicarbonate improved symptoms, though not mortality (Hobel et al, 1972). While Reid, Tunstall and Mitchell (1967) demonstrated that assisted ventilation reduced the mortality. The introduction of continuous positive pressure (Gregory et al, 1971) and the subsequent modifications appears to have reduced the mortality significantly. Allen et al (1977) presented evidence that continuous positive airway pressure (CPAP) used early in the disease, appeared to reduce the mortality. They also further analysed data from all the available clinical trials and concluded that early CPAP was a significant advantage. Detection of potential cases of RDS by the shake test (Clements et al, 1972) was clearly a major advance. The antenatal administration of glucocorticoids in threatened premature delivery has proved to be a significant advance in the prevention of idiopathic respiratory distress (Liggins and Howie, 1972).
It is hoped that RDS will become less of a scourge by the increasing application of new preventive and therapeutic measures.

(13) Oxygen Therapy

The place of oxygen therapy in the care of the newborn infant has been under close scrutiny since the association of excess oxygen administration with retrolental fibroplasia was demonstrated. Crosse and Evans (1952) showed that reduction in the level of oxygen administration to pre-term infants virtually abolished retrolental fibroplasia. As a result oxygen was used with much greater caution in the management of respiratory distress. Avery and Oppenheimer (1960) subsequently demonstrated that the death rate rose during the period of more limited use of oxygen. Their data are suggestive of a causal relationship but do not include details of sex, mean and standard deviations of birth weight and menstrual age, or subsequent statistical analysis, which should be available in such a study. It has been accepted that the risk of retrolental fibroplasia is low at oxygen concentration below 40 per cent, though higher concentrations may be required in babies with cyanosis. Under such circumstances it is very important to monitor the partial pressure of the blood PaO_2 (Robertson et al, 1968). Such procedures incur the slight risks associated with umbilical artery-catheterisation.

After the administration of high concentrations of oxygen over long periods to adult patients with normal lungs, who subsequently died of unrelated non-pulmonary conditions, there was evidence of oxygen toxicity at autopsy (Pratt, 1958). The changes noted were pulmonary congestion, fibrosis and capillary proliferatinn. However, all the patients were adults and the data must be interpreted with care, since the age of the patient may have a bearing, at least in short-term oxygen therapy. Thus animal experiments (Smith et al, 1932) show that young rats have only minimal changes with short-term high concentrations of oxygen when compared with old animals.

With prolonged administration, however, the changes were similar irrespective of age.

Incubators that can maintain high concentrations of oxygen and analysers for measuring environmental and blood oxygen levels are now commonplace in special care units for the neonate. The value of such equipment can be diminished by the continued use, however well intentioned, of such crude measures as directing a stream of oxygen onto the face of an ill infant. Such a manoeuvre can result in a reflex rise in the metabolic rate of a neonate (Mestyan et al, 1964).

The judicious use of oxygen has undoubtedly been of the utmost benefit to the ill neonate but care is necessary and there is still much to learn.

(14) Temperature

Maintaining the body temperature within the neutral range is vitally important to the ill newborn. It has been shown by Brück (1968) that oxygen uptake is at a minimum when the body temperature is within the neutral range. Evidence based on mortality rates from several controlled trials supports the experimental findings. Silverman, Fertig and Berger (1958) compared survival rates between babies maintained at two different temperatures. The infants at an environmental temperature of 31.7°C (low by modern standards) were compared with a control group at 28.9°C. The controls had a higher mortality rate which may in part be due to a lower mean birth weight and the inclusion of fewer females, factors which tend to favour a higher mortality rate. Day et al (1964) reported the improved survival of infants between 800 - 1599 g with skin temperatures maintained at 36°C as compared with infants kept in environments of 31.8°C. Buetow and Klein (1964) found that the major improvement in the mortality rates induced by higher temperatures was in infants weighing between 1251 - 1500 g at birth. To derive the maximum advantage of optimum temperature control in future studies of survival, the index infants should clearly be kept within the neutral temperature range. Jolly, Molyneux and Newell (1962) showed improved survival, especially of babies of very low birth weight, when nursed in warm environments. Recent research of comparing long-term follow-up of babies from different years from the same nursery has shown that babies grow at a greater rate when nursed in a warm environment (Glass, Silverman and Sinclair, 1968). Davies and Davies (1970) showed that a group of babies fed and maintained at lower temperatures in 1961-64 had smaller head circumferences at follow-up than a subsequent group reared at higher temperatures in 1965-68. It would appear that the maintenance of an adequate temperature is mandatory in the management of low birth weight infants if mortality and morbidity rates are to be reduced. It is important that the correct temperature should be selected as apnoeic attacks have been reported (Daily, Klaus and Meyer, 1969) in very low birth weight infants maintained at the upper limits of the neutral temperature range.

(15) Conclusion

Significant advances have been made in the management of neonatal asphyxia, jaundice, infection, haemorrhagic disease and hypoglycaemia, and in the maintenance of nutrition and body temperature. Improvements in the management of apnoeic attacks, cerebral haemorrhage, hypotension and idiopathic respiratory distress syndrome have been less decisive. No major advance has occurred in our understanding and treatment of intraventricular haemorrhage.

Though great improvements have taken place in the management of the infants of low birth weight, birth and neonatal life still remain an uncharted and hazardous experience for this small but important group of infants.

CHAPTER II

LOW BIRTH WEIGHT

There has been considerable controversy over the outcome of LBW infants. Capper (1928 b) showed that one third were functioning at their expected level while later Drillien (1964) and Lubchenco et al (1963) continued the gloomy outlook. Mohr and Bartelme (1934), Douglas (1956) and Rawlings et al (1971) have reported more favourably upon the prognosis. The last authors implied that improved standards of care were responsible for a significant reduction in the long term morbidity, whilst Douglas felt that earlier workers had failed to take into account the importance of the social background of the LBW infants. The Robinsons (1965) summarised the problem, when they stated "aside from physical size and major physical defects, social class assumes much more importance than does birth weight (BW) in determining a child's developmental prognosis".

DIFFICULTIES OF PREVIOUS STUDIES OF LOW BIRTH WEIGHT

There has been a tendency in past studies to consider only one aspect of the syndrome of LBW. Such a position has usually been forced upon the investigators by the design of their study. A brief discussion of the literature will be undertaken to highlight the difficulties which have influenced the results of previous studies and have given rise to conflicting conclusions. It is hoped that from such a discussion a framework for future studies can be outlined.

(1) Definition

Though the association of premature birth with subsequent handicap appeared obvious to the early investigators it proved extremely difficult to define prematurity in terms of menstrual age. Numerous studies testify to the inaccuracies arising when the date of the last menstrual period (LMP) was used. It seemed reasonable to assume that fetal weight gain was related to fetal age. However, it was not without reservations that such a concept became embodied in the statistically convenient 1948 WHO (Bulletin World Health) definition of prematurity, i.e. a birth weight of 2500 g or less and or a gestation period of 37 completed weeks. Both Capper (1928b) and Rosanoff and Inman-Kane (1934) were fully aware that fetal growth rates were not uniform and that term babies of impaired growth were included in such a definition.

In the majority of studies, observations were made on infants weighing 2500 g or less at birth. A small but significant number studied babies of lighter weights - 1500 g or less (Lubchenco et al, 1963; Rawlings et al, 1971). Such a choice seems reasonable since nearly 95% of infants less than 1500 g are delivered before 34 weeks (Thomson, Billewicz and Hytten, 1968).

The introduction of a definition depending on a precise body weight (Alm, 1953) excluded vague terminology and enabled comparisons to be made between different studies. None the less, the recent widespread recognition of the results of intra-uterine growth retardation (IUGR) has further confused matters and made the confirmation of the LMP mandatory if the babies with IUGR are to be adequately studied.

(2) Sample

(i) Weight

In previous studies many different birth weights have been employed as the criterion for selection. They have included 1000 g (Dann, Levine and New, 1958) (rather unsatisfactory, as minimal postnatal weight was included), 1500 g (Lubchenco et al, 1963; Rawlings et al, 1971); 1800 g (McDonald, 1967) and 2500 g (Mohr and Bartelme, 1934; Drillien, 1964; Douglas and Mogford, 1953, and Knobloch et al, 1956). Studies utilising weights of 1500 g show a high percentage of the complications of early delivery whilst studies utilising a cut-off point at 2500 g are heavily influenced by the effects of intra-uterine growth retardation.

(ii) Length of gestation

Due to the unreliability of estimating the LMP, no study has selected infants on the basis of menstrual data. It is a serious weakness of previous studies that no attempt has been made to confirm clinically the date of the LMP.

(iii) Race

The studies of Dann, Levine and New (1958), Lubchenco et al (1963) and Rawlings et al (1971) included infants of different races. The study of Knobloch et al (1956) removed the influence of race by the use of matched controls for this variable. Mohr and Bartelme (1934) selected only white infants but a third of their sample was of Jewish extraction. Alm (1953), Douglas and Mogford (1953) and Drillien (1964) studied racially homogeneous groups of infants.

Ethnic differences materially affect BW (Anderson Brown and Lyon, 1943). Thus for example, Geber and Dean (1957) concluded that negro babies were more advanced neurologically than Caucasian babies. The results of intelligence testing show ethnic differences which clearly stem from the complex social and biological influences associated with race. In such circumstances it would seem preferable to either remove or control the influence of race in LBW studies.

(iv) Geographical Area

The geographical basis of sampling, whether national, local or drawn from hospital or clinic, will profoundly influence the conclusions.

(A) National Sample

Douglas and Mogford (1953) enrolled a national sample of all LBW infants delivered during a one-week period in 1946. The advantage of the large numbers obtained by such a method is counter-balanced by administrative difficulties and variations in standards of care between centres.

(B) Local Area

Knobloch et al (1956) selected from a local geographical area all infants with birth weights of 1500 g or less and a selected sample of those delivered with a BW of 2500 g or less. Further selection was introduced by enrolling only those infants who attended the nine-month follow-up clinic. Though convenient, the enrolment of only the attenders may introduce serious bias.

(C) Hospital

Some hospitals serve clearly defined catchment areas but, due to the structure of the community, unintentional selection of certain segments of the population may take place. Robinson and Robinson (1965) from a hospital sample, selected a group of those enrolled in a special care programme. Drillien (1958) utilised infants delivered in two Edinburgh hospitals and required the mothers to be resident in the city at the time of birth as well as for the next six months. Other hospitals act as referral centres because of their specialist expertise (Dann, Levine and New, 1958; Lubchenco et al, 1963; Rawlings et al, 1971). Studies will then be biased towards those infants likely to survive the journey to the hospital: moreover, the hazards of the journey may have adverse effects which introduce further bias.

(D) Clinic

Samples drawn from hospital clinic populations will show a high incidence of pathology due to the natural tendency for disease to be referred to hospital. A high incidence of handicap was noted by Barlow (1945) from a sample obtained from both clinic and private practice.

(3) Controls

The earlier studies of LBW were poorly designed epidemiologically. From these, it became apparent that controlled studies were required to separate the various factors implicated in the syndrome of LBW.

(i) Non-matched controls

Alm (1953) selected as a control (BW 2760 - 3750 g) the next male infant in chronological order on the register. Though such studies helped to clarify the general picture, it proved difficult to study in depth the areas which appeared important. For example, the effects of slight environmental differences upon IQ may not be apparent unless case and control are matched for social class.

(ii) Matched controls

(A) Sibling controls

When selecting matched controls, it is desirable to control for both genetic and environmental factors. The use of siblings (Mohr and Bartelme, 1934, Dann, Levine and New, 1958, Fitzhardinge and Steven, 1972) appears to be the best way of achieving this but serious difficulties arise. For example, less than half of Mohr and Bartelme's (1934) sample had siblings.

In addition, the position within the sibship appears to be important. For example, Althus (1966) concluded that ordinal position at birth appears to be related to significant social parameters.

(B) Selected Variables

Certain factors, such as social class, have a profound influence on both BW and the indices subsequently used at follow-up, e.g. IQ. By the use of matched controls it is possible to study the effects of BW independently of social class. Despite careful matching, minor difficulties may exist (Douglas, 1960) but it is in just this situation that the data are capable of more detailed analysis which may subsequently throw light upon important differences between LBW infants and their matched controls.

(a) Social Class

It is essential to take account of social class in the study of LBW. For example, intelligence, amongst other variables, appears to be related to social class (Social implications of the 1947 Scottish Mental Survey). In an attempt to negate this influence, Douglas and Mogford (1953) controlled for social class, using the Registrar-General's classification, but subsequently found that, even with careful matching (Douglas, 1960) the social background of his LBW group was inferior. Robinson and Robinson (1965) matched for occupation whilst Knobloch, et al (1956) used a poorly-defined criterion of median rental. It may be possible to eliminate the major influence of social class by adequate matching and then to investigate in more detail any more subtle differences in the environmental background between LBW infants and their matched controls.

(b) Ordinal Position in the Family

The ordinal position affects the child in a number of ways. Mortality at birth is lowest in the second born (Butler and Bonham, 1963): intelligence appears to decrease with increasing family size (Social Implications of 1947 Scottish Mental Survey). It seems reasonable to remove these small but possibly cumulative influences by adequate controlling. Thus, Douglas and Mogford (1953) controlled for ordinal position, whilst Knobloch et al (1956) utilised parity.

(c) <u>Sex</u>

Few studies have matched for the influence of sex, notable exceptions being Douglas and Mogford (1953) and Robinson and Robinson (1965). Females are lighter at birth than males (Thomson, Billewicz and Hytten, 1968), have a lower mortality (perinatal mortality) and have different IQ scores (McDonald, 1967). It is therefore important to control for this variable.

(d) <u>Legitimacy</u>

Illegitimacy, like LBW, is a complex and poorly-understood subject. A number of observers have removed the complicating effects of illegitimacy in order to simplify the study of LBW (Douglas and Mogford, 1953).

(e) <u>Multiple Pregnancy</u>

Earlier studies (Drillien, 1964; Lubchenco et al, 1963) included multiple pregnancies because of the high incidence of LBW infants amongst such pregnancies.

The problems of delivery, the special nature of the sibship and the difficult task of obtaining adequately matched controls have persuaded recent researchers, e.g. Douglas and Mogford (1953) to exclude multiple pregnancies from their studies.

(f) Miscellaneous Variables

Other characteristics, e.g. place of birth, and season of birth, have been taken into consideration (Knobloch et al, 1956). The effect of place of birth can be eliminated by making the original selection from a clearly-defined geographical area. The problems of matching are multiplied as the number of variables increases. It may ultimately be possible to match any infant for almost any number of variables but a time limit is imposed on most studies even if it is only by the financial resources available!

(C) Conclusion

To the clinician it is obvious that LBW infants are at a serious disadvantage. Due to the multifactorial nature of the problem, randomly controlled epidemiological studies are only capable of making limited contributions to knowledge. By the use of matched controls it is possible to carry out more exact comparisons between patients in the search for adverse factors in infants of LBW.

(4) Methodology of Assessment

When considering the techniques used in previous studies, a number of serious methodological deficiencies become apparent. They are discussed under the following categories:

(i) Post-Conceptual Age

The results of follow-up examinations during infancy and early childhood are seriously biased against pre-term infants unless adjustment has been made for early delivery. Gesell (1928) originally postulated the need for such correction from a study of two infants. Shirley (1938), using body weight rather than gestational age, considered that babies weighing under 4 pounds were retarded by a month or more through the first 18 months of life but those weighing between 4 to 5 pounds, closed the gap by 9 months of age.

(ii) Age at Assessment

Psychometric tests during the first two years of life measure mainly motor function whilst in childhood they test language and problem-solving abilities. Due to the construction of the tests, serious errors are likely to occur if comparison of results is undertaken between children of different ages. Capper (1928 b), without the aid of formalised tests, reported on the outcome in children with an age range from 1 - 19.5 years. Recent studies have been more sensitive to the inaccuracies introduced by assessing children at different ages (Douglas, 1960); attempts have been made to examine the children at a uniform age and those not examined at the chosen age have been excluded.

(iii) Loss

Loss of patients from the sample may profoundly influence the results. Dann, Levine and New (1958) did not follow up 43 out of their population of 116 infants and yet 19 of the 43 were known to be mentally retarded. The early studies had considerable losses from their series - for example, only 53 per cent (Capper 1928 a), and 67 per cent (Lubchenco et al, 1963 and Saint-Anne Dargassies, 1977): such losses would seriously influence the validity of their results. More recent studies have made stringent efforts to obtain a maximum yield at follow-up - 95.8 per cent (McDonald, 1967), 94 per cent (Rawlings et al, 1971), and a less satisfactory yield of 79 per cent by Drillien (1969) at 11-13 years. Sample loss is inevitable but it clearly must be reduced to the minimum possible.

(iv) Intellectual

In the early studies of LBW (Capper 1928 b), the assessment of intellectual ability was based upon the child being in the appropriate school class for his age. In recent studies, the assessment of IQ has been based on the use of standard tests, e.g. Stanford Binet test (Robinson and Robinson, 1965). Though such tests can be uniformly administered, they are not without their limitations. Gesell development schedules are more likely to detect motor handicap than Binet's examination, since the former is more dependent upon manual dexterity. IQ tests estimated before the age of two years may have a zero correlation (Jones, 1954) with subsequent IQ (presumably because tests measure mainly motor function before two years of age). In the past, measurements of IQ repeated over a period have been believed to remain constant. However, Neff (1938) considered that individuals might show a twenty point change over the short term and up to a fifty point variation where there was a lengthy interval.

The use of intelligence tests has many advantages over the subjective methods used in a number of previous studies. Care, however, must be exercised and the limitations imposed by the use of formalised tests must be kept in mind.

(v) Environment

In a study of the children of canal boat workers, the influence of poor environment upon IQ results was noted (Educational Pamphlets 1923). In this particular study the lack of school attendance was also a serious contributing factor. Neff (1938) felt that 20-30 points on an IQ score may be lost on average by continual exposure to a poor environment. Douglas (1960) noted that children with interested parents scored higher in their work even after standardising for social class. Douglas (1956) noted the enhancing effect of their environment upon the vocabulary and intelligence of children born into the higher social classes. Robinson and Robinson (1965) concluded that apart from major physical defect, social background assumes more importance than BW in a child's subsequent development. It is obvious that environment must be taken into account when considering the long-term results of LBW studies.

(vi) Statistics

As the problems of LBW have become more complex, it has become increasingly important to subject studies to statistical analysis.

Alm (1953) was one of the earliest investigators to use statistical methods in analysing his data and subsequently Douglas (1956), Drillien (1958), Knobloch et al (1956) and Robinson and Robinson (1965) employed a variety of techniques. Though statistical analysis usually shows that LBWs are inferior to their controls, it is doubtful whether such a simple interpretation is justified without taking into account the highly atypical associations of LBW.

(5) Biochemical Information

The role of biochemical abnormalities in the production of handicap was not fully appreciated until the early 1960's. As a consequence, detailed records of hypoglycaemia, hyperbilirubinaemia, hypoxia and dehydration were kept to enable biochemical data to be related to subsequent handicap.

(6) Intrauterine Growth Retardation

Many of the earlier studies did not recognise the importance of impaired fetal growth though a few workers (Capper, 1928 b) were clearly aware of it. Occasional subsequent references can be found in the literature but it was not until the 1960's that the problem was widely recognised. Further understanding has been relatively delayed due to the difficulty of reaching a suitable definition. With awareness that intrauterine growth retardation may profoundly influence long-term development, all recent studies have taken great care to verify gestational age to enable impaired fetal growth to be defined.

(7) Conclusion

Serious methodological problems have arisen in previous LBW studies. Greater care over the selection of children of similar age at follow-up, sample loss, intellectual assessment, environmental influences and the use of statistical techniques should improve the quality of future studies.

RESULTS OF PREVIOUS STUDIES

The difficulties encountered in previous studies have already been considered. In this section a short outline of the results from the more important of these studies will be discussed.

(1) Mortality

That mortality rates of LBW infants are higher than those of infants of normal weight at birth is well documented by many studies and in health service statistics. This has indeed been one of the main reasons why the attention of clinicians had been directed to the problem.

(2) Growth

There has always been debate concerning the ultimate growth potential of LBW infants. Capper (1928 b) thought that LBW infants, even at puberty, were still below their expected height and weight. In a controlled study, Alm (1953) showed that the full potential for height and weight of LBW infants was not even reached by adult life. A shorter ultimate stature following LBW would be expected from the association of LBW with low social class. The recent report of critical periods of cell growth (Medovy 1967) suggests that ultimate stature might be reduced if infants were affected by abnormalities of intrauterine growth resulting in reduction of the cellular population of the fetus.

(3) Chronic Handicap

In early studies the category of handicap comprised physical disabilities ranging from convulsions to cerebral palsy. More recent studies (Drillien, 1969) have extended the concept of handicap to include mental and behavioural disturbances as well as physical disability.

A wide range of incidence has been reported, e.g. Lubchenco et al (1963) noted that 43 out of 63 had physical or mental handicaps (22 spastic diplegia and 16 retrolental fibroplasia) in a group with BW 1500 g or less. McDonald (1967) found a 6.5 per cent incidence of cerebral palsy, 3.7 per cent of retrolental fibroplasia and 1.3 per cent of cataracts in her study of infants with a BW of 1800 g or less. Dann, Levine and New (1958) reported that 9 out of 73 infants had a variety of severe physical defects, while of the remainder 38 had serious opthalmic defects.

In the earlier studies the correlation of subsequent handicap with LBW was very high.

(4) Mental Handicap

LBW is associated with five times the incidence of impaired intelligence, as shown for example by Rosanoff and Inman-Kane (1934) in their study of institutionalised mental defectives. It has sometimes proved difficult to compare the results of studies because different authors have adopted different criteria. Thus McDonald (1965) chose as the dividing line an IQ of less than 70, while Dann, Levine and New (1958) selected a figure of less than 80.

A number of workers in some of their analyses have excluded cases with an IQ of less than 50 on the grounds that they represent an abnormal population (McDonald, 1967). Drillien (1969) agreed with the finding of an impaired IQ in LBW and Douglas (1960) on the other hand, felt that LBW infants became more handicapped, as measured by IQ, with the passage of time and he attributed such a trend to the unfavourable social background of the infants.

More recent study of infants born in the late 1960's and early 1970's suggests a marked decline in the incidence of handicap. In a sample of 72 surviving infants below 1500 g, (Rawlings et al, 1971) noted that 7.4% were abnormal whilst 5.9% were classified as doubtful. Dweck et al (1973) reported that 11 out of 14 infants with a birth weight between 960 g and 1100 g were neurologically normal at follow-up carried out between 11¼ and 33½ months. There has also been a significant decline in the incidence of spastic diplegia between 1961-64 and 1965-70, falling from 10.3% to 0 (Davies and Tizard, 1975).

Despite these impressive advances recorded in the last few years, Douglas and Gear (1976) have reported very favourable results of infants with birth weights below 2000 g identified in 1946 and managed either at home or in hospital.

There is little doubt that impaired mental ability is associated with LBW but at present the precise aetiological relationships remain obscure.

(5) Intrauterine Growth Retardation

Since the turn of the century, there have been a number of scattered references clearly documenting IUGR both in the medical, Capper (1928 b) and lay literature Huxley (1932). However, it is only during the last 10 years that impaired fetal growth and its consequences have been investigated in any great depth. Despite the great interest and consequent work, IUGR is still bedevilled by the lack of a suitable definition. With the growing awareness of the needs of the growth retarded baby, particularly during the perinatal period the prognosis for such infants is considerably improved over the last 10 years.

Probably the earliest population study was carried out by McDonald, (1967) who found an excess of cataracts, convulsions and mental retardation in a cohort of light-for-date (LFD) infants weighing less than 1800 g. In a study of undersized term infants of 2000 - 2700 g (Babson and Kangas, 1969) pre-school intelligence was 3 points lower than controls. Weiner (1970), in a retrospective study of low birth weight, found that intellectual development at 8 - 10 years of age was similar between small-for-dates infants and those of short gestation. Churchill (1965), comparing the intellectual outcome of 50 pairs of twins with discrepant weights, noted that the undergrown twin performed significantly less well than its heavier sibling. Inspection of their data shows rather small differences, i.e. less than 5 points between the pairs.

More recently specific studies have been designed to assess the effects of impaired fetal growth and intelligence. In a prospective study of 96 full term small-for-dates infants, minimal cerebral dysfunction was diagnosed in a quarter, and a high incidence of EEG abnormalities and speech difficulties were found (Fitzhardinge and Steven, 1972). In a sample of growth retarded babies with birth weights below 1500 g, Davies (1975) found significant differences in full scale and performance IQ tests when compared with appropriately growth infants. The comparison of a group of small-for-dates and appropriately growth preterm infants may not necessarily be valid as the background between the two groups may be very different. The environmental factors might have greater bearing on IQ than fetal influences. In the most comprehensive study to date Neligan et al (1976) conclude that intrauterine growth retardation may cause severe infrequent handicap or frequent mild handicap. This excellent summary of the situation leaves unanswered the relative contribution of medical and social factors in the damaging effects of intrauterine growth retardation.

(6) Environment

It is well known that poor environment and LBW are closely intertwined. Numerous studies, e.g. that by Blegen (1952) utilising measures of social impairment, have noted the high incidence of LBW when the environment is poor. Douglas (1960) highlighted the problem when he showed in a carefully controlled study that LBW infants came from less favourable social backgrounds than controls. Robinson and Robinson (1965) concluded that, apart from physical defect, social class is the most important influence on the child's ultimate development and that it is in this light that the problems of a child's environment must be viewed.

(7) Behavioural Problems

It is well documented that LBW infants have a higher incidence of behavioural problems (Benton, 1940). Both Douglas (1960) and Drillien (1964) noted a higher incidence of problems at school. Recent studies have shown a considerable fall in the incidence of physical handicap (Rawlings et al, 1971) and it may be hoped that in future there will be a parallel decrease in behavioural handicap.

Conclusions

The results of previous studies are described. They show that there has been a reduction in the incidence of mental and chronic physical handicap in recent years. To put these advances into perspective, one must remember the work of Hess (1953) on the outcome of babies with birth weights less than 1250 g, and a recent report by Douglas and Gear (1976) concerning the favourable outcome of infants below 2500 g from a national sample born in 1948. These data suggest that iatrogenic factors made an important contribution towards the high morbidity rates recorded in many reports of children born in the 1950s.

Intrauterine growth retardation is frequently associated with mild handicap subsequently and occasionally with severe handicap. Unfortunately this simple summary does not clarify the relative contribution of medical and social factors to the adverse effects of intrauterine growth retardation.

CHAPTER III

PLAN OF THE PRESENT STUDY

(1) Reasons for Undertaking a Study of Low Birth Weight

It was apparent from previous studies of low birth weight that a wide range of sequelae has been recorded at follow-up examination. When considering babies of similar birth weight, the incidence of subsequent handicap has ranged from 68 per cent (Lubchenco et al, 1963) to 13 per cent (Rawlings et al, 1971). This diversity of results indicated that further study of outcome was highly desirable, especially in view of the changed pattern of perinatal care outlined in Chapter 1. In Chapter II the difficulties encountered in previous studies have been discussed at length. It was concluded that in any prospective investigation, three areas of study were of the utmost importance, viz (i) Sample Selection; (ii) Environmental Influences; and (iii) Perinatal Problems.

(i) Sample Selection

It was recognised that it is very important to enrol cases from a clearly-defined geographical area of known population structure, in order to avoid the dangers of bias introduced by the use of hospital or clinic populations. The use of controls is mandatory in any study due to the complexity of factors contributing to low weight at birth. Careful matching enables detailed comparisons to be made between cases and controls: it should take account of features which influence fetal growth, e.g. parity, sex of the infant, and maternal height and smoking characteristics. These characteristics - except sex of the infant - will, in addition, reflect the socio-economic background of the child and, when considered in conjunction with social class, as determined by paternal occupation, will enable a detailed picture of the socio-economic background to be obtained. By matching for these variables it is possible to hold them constant when examining the influences of other factors in the genesis of LBW.

(ii) Environment

Environment has a continuous effect on pregnancy, delivery and the subsequent development of the child. Due to its complexity, scant attention has been paid to the problem in previous studies except for the limited use of social class as an indicator. It was obvious that better documentation of environmental detail was essential in any future study.

(iii) Perinatal Period

(A) Clinical details

It is widely accepted that improving standards of newborn care result in a reduction in neonatal mortality rates. Most previous studies have ignored this important fact, though recently some authors have given it due consideration, e.g. Rawlings et al (1971), Davies and Davis (1970. It was appreciated that any future study of LBW would require to pay careful attention to documenting the details of clinical care.

(B) Intra-uterine Growth Retardation

IUGR has become one of the major subjects of interest in the field of neonatal paediatrics. Despite extensive work, however, there is still a lack of adequate definition, clinical description and long-term follow-up of affected infants. It was considered that further study should attempt to clarify this area.

METHODOLOGY

(2) Background to the Study

Aberdeen, with a population of approximately 180,000, is an historic city whose position as the centre of a large area in north-east Scotland relatively isolated by mountains has resulted in an ethnically homogeneous population. At the time of the study it was the third biggest city in Scotland and depended largely upon its traditional industries of agriculture, fish, granite and the manufacture of paper. In addition a university and a number of colleges and research institutes provide employment within the city. Oil was discovered in the North Sea only after the setting up of the study and therefore its obvious social impact has not influenced the original sample.

Aberdeen is unusual in that its medical and health services are centralised to a very high degree. For example, 99 per cent of all births take place in one maternity hospital, with its three associated small nursing homes. The stillbirth rate (11.5), neonatal mortality rate (10.5) and infant mortality rate (16.5) (averaged for the two sample years) are very low for a northern industrialised city. With these various advantages, Aberdeen is well suited to a population study of LBW infants and their matched controls.

It was planned to collect from 1st July 1969 a prospective, one year cohort of all singleton legitimate low birth weight infants (2500 g or less at birth) and their matched controls (greater than

2500 g at birth) born to mothers residing in the city and suburbs of Aberdeen. Of the total of 198 singleton LBW births (Table III 1), 23 died and 26 were rejected; Table III 2 shows the distribution of those rejected. Students were not included due to the problem of classifying their ultimate occupational grouping and 4 children of hospital staff were excluded on sociological grounds because of the personal nature of the questions asked.

After the exclusions, the cohort for the one year period totalled 145 infants. A further 4 infants were included as part of the special sociological study. They were infants of Social Class 1 primigravida who were included after the one year period due to the scarcity of low birth weight babies in this social class.

(3) Selection of the Controls

A control infant was enrolled as soon as possible after the delivery of each LBW infant. In all, 7 mothers refused to allow their babies to be included as controls and in these instances the next infant delivered with suitable matching characteristics was enrolled.

(i) Matching factors

Five factors were selected for matching: paternal occupation (indicating social class) ordinal position in the family, maternal height, maternal smoking habits and the sex of the infant.

(A) Social class

Matching of the controls by paternal occupation at the time of delivery was carried out according to the General Register Office classification of occupations (1960). Forty-one per cent of the LBW cohort were from Social Classes IV or V compared with the Aberdeen Maternity Hospital distribution of 26 per cent (Table III 3). It is well known that LBW is skewed to the lower social classes. In the later stages of the study, to allow completion of the control sample, the categories of social class were broadened. Social classes I and II and certain occupations in IIIa (not shop assistants) were combined together, as were social classes IV and V.

(B) Ordinal position in the family

As one of the controlling variables for the sociological aspect of the study, ordinal position was chosen in preference to pregnancy number. Satisfactory matching (Table III 4) was obtained except in cases from families with four or more children. Aberdeen births are approximately half the national average of this group which accounts for the difficulty in matching.

(C) Maternal Height

Control infants were selected from mothers in similar height categories or to within two inches.

Small less than 5ft 1in (less than 155 cm)

Medium 5ft 1 in to less than 5ft 4in(155cm-162cm)

Tall 5ft 4in and over (greater than 162cm)

The mean height of the control infants' mothers was slightly greater despite attempts at stringent controlling (Table III 5). This is because of the higher number of very short women in the group.

(D) Maternal smoking habits

Though opinion seems to be divided on the influence of smoking on birth weight, in the present study attempts were made to control this variable. A number of difficulties arise which relate to smoking. The reliability of the history, and the amount and timing during pregnancy, as well as the question of inhalation. In categories for which it proved very difficult to obtain controls, smoking was the first variable to be dropped. Despite efforts to match for smoking habits, the mothers of the LBW infants tended to be heavier smokers than the mothers of the control infants (Table III 6).

(E) Sex of the infant

As females have both a lower birth weight (Thomson, Billewicz and Hytten, 1968) and a lower mortality rate, they tend to be over-represented in LBW studies. The present study shows an equal distribution by sex (74 male : 75 female), probably a chance variation due to the relatively small numbers. The favourable prognosis for females is seen by their preponderance at weights under 1500 g (11/13), see Table III 7.

(ii) Accuracy of Matching

For the three factors affecting later social development of the child - social class, ordinal position in the family, and sex of the infant - adequate matching for ordinal position in the family was obtained in all but one case. This one, though easy to match for biological factors, presented considerable sociological matching problems, since there were already two adopted children in the family. Of the maternal biological factors influencing fetal growth - smoking and height - the former proved difficult to match exactly in five cases. This is hardly surprising in view of the well-known vagaries of maternal smoking history. In the twelve cases incorrectly matched for height, the division into the three broad categories tended to exacerbate the problem. An attempt was made early in the study to narrow the height difference by matching to within two inches (5 cm) irrespective of the broad categories of tall, medium or small. The net result was to produce a more accurate match in 25 of the cases (see Table III 8).

The problem of the grand multipara (para 4+) posed special matching difficulties. Due to the family planning policy in the area, the number of grand multiparae in Aberdeen has sharply declined in recent years. It was anticipated that selection of controls for LBW infants from such pregnancies would be extremely difficult. In the event, the reverse was found to be the case, as a result of an initial policy decision to consider para 4+ as a single group for the purposes of matching for ordinal position in the family. An excellent degree of matching for the other characteristics was obtained in this extremely atypical group.

(iii) Birth weight

The distribution of birth weight amongst LBW infants and controls is shown in Table III 9.

The mean weight of the controls is lower than that of the normal population due to the selection factors inherent in the study, e.g. the bias due to low social class.

(iv) Gestational age

The very low certainty rate amongst mothers in the present studies reflects the more stringent definition imposed as well as the increasing use of "the pill" in recent years.

Of those mothers of LBW infants who were certain of their LMP only 8/91 were delivered before 30 completed weeks whilst 47/91 were delivered after 36 completed weeks. The controls were for all practical considerations delivered at term (see Table III 10).

(4) Clinical Measurements

A prospective study of a complete population of LBW infants over a period of one year presents considerable staffing difficulties if all the infants are to be adequately examined. Two doctors with paediatric experience were concerned with making the clinical observations and collecting samples for biochemical analysis; the major part of the work was undertaken by J.I.C., while E.J.D. was responsible for the remainder, including many of the examinations for neurological maturity.

The collection of clinical data was carried out to describe:-

(i) physical appearance

(A) general characteristics

(B) apparent gestational age

(C) anthropometric measurements

(ii) the clinical progress of the baby

(A) clinical events

(B) biochemical changes

(i) Physical Appearance

(A) General characteristics

It was decided to describe each baby in terms of its appearance, length of hair, nutritional state and the presence of congenital abnormalities; 81% of the general examinations were carried out by J.I.C. (Table III 11).

(B) Estimation of gestational age

(a) External physical characteristics in the Estimation of gestational age

Estimation of gestational age was carried out by the method of Farr et al (1966). Great care was taken to assess each individual item on the score rather "than to look at the baby as a whole".

Knowledge of the maternal LMP was scrupulously avoided at the time of the examination and decisions as to whether the gestational age was correct were made by an independent obstetrician. It was considered that corroboration by the examiner of the date with the mother after the examination might undesirably influence the result. The number examined by each member of staff is shown in Table III 12.

(b) Neurological estimation of gestational age

The estimation of gestational age by the neurological method was carried out according to Dubowitz, Dubowitz and Goldberg (1970) and depends upon the concept of tone. The distribution of cases examined by the two observers is shown in Table III 13. Due to the number of omissions no further analysis was proceeded with in this thesis.

(C) Anthropometric measurements

Measurements were made in triplicate of occipito-frontal circumference, crown-heel length, crown-rump length, thoracic circumference, and skinfold thickness in all babies. Table III 14 shows the number of examinations omitted and the percentage carried out by J.I.C.

(a) Occipito-frontal circumference

Errors occur in measurement due to difficulty in distinguishing the largest diameter and to caput formation. Head circumference is correlated with brain volume but alterations in the curvature of the skull, e.g. a receding forehead, may conceal the true volume of the brain.

(b) Crown-heel length

Infants were placed in a measuring box - see below - on a paper towel both for hygienic purposes and to assist sliding. Their heads were held by an assistant in Frankels plane against the fixed headboard. The examiner straightened the legs at the knees, brought the foot board into position and made the measurement. It was considered that the examiner had more control of the legs of the infant by this method. Difficulties were encountered in babies with orthopaedic deformities and in those with severe illness which prevented removal from an incubator.

(c) Crown-rump length

Crown-rump measurement presented less technical problems than crown-heel. The nutritional state of the infant, as reflected by the size of the buttocks, seemed to have a significant influence on the result.

(d) Thoracic circumference

Variations in respiration and "winging of the scapulae" contribute to the difficulties in the measurement of the thoracic circumference. Despite these theoretical considerations, thoracic circumference was accurately repeatable.

(e) Skinfold thickness

The cumbersome nature of skinfold calipers has necessitated the production of simplified instruments (Verel and Kesterven, 1960). Despite the use of these, the measurement of skinfold thickness over the chest and the thigh proved difficult, whilst abdominal estimations had to be abandoned because of the inability to pick up an adequate fold in the presence of abdominal distention or when umbilical catheters were in situ. Of the abdominal caliper readings 11/24 were omitted due to an umbilical catheter being in situ preventing adequate estimation. No difficulties were encountered in measuring tricep and scapula skinfolds.

Five sites were selected as above and have been outlined by Farr (1966) but abdominal skinfold was discarded for the above reasons. Care was taken to zero the calipers for each individual reading. Due to the small measurement and the magnification required to enable the result to be read, particular attention had to be paid to reading the caliper gauge at right angles. The role of oedema in newborn caliper measurement has received scant attention. It was considered that the presence of oedema might have a serious influence on the readings but it proved impossible to quantitate this suspicion objectively. The poor degree of accuracy on repeated measurement by the same observer limited the use of these calipers as an indicator of the amount of subcutaneous tissue. In broad terms caliper measurements were employed to quantitate the clinical impression obtained by palpation of the extent of tibial subcutaneous tissue loss in the absence of oedema.

(D) Statistical analysis

The statistical analysis of the inter observer comparisons was carried out by Mrs. Shirley Hart of the Medical Research Council Sociology Unit at Aberdeen. The general statistical analysis was performed by Mrs. P. Easton of the White Top Foundation. The "t" test for pairs was used in some instances but analysis of variance (ANOVA) was used in the majority of cases as it was desired to compare statistically the results between two examiners (E.J.D. and J.I.C.), each of whom had made two separate examinations of a given baby at different times on the same day.

(a) Total maturity score

Comparison of results made by the same examiner at different times of the day are liable to be influenced by memory. Therefore only one examination was made by each examiner for the maturity score and the result was statistically analysed by the "t" test for pairs. The standard deviation of the difference is 2.47 which at between 1 - 14 degrees of freedom is significant at less than 5 per cent. Due to the structure of the maturity score, the clinical relevance of this difference between examiners varies over the range of gestational ages. A difference in the maturity score of 2.47 at shorter gestational ages 32 weeks represents a discrepancy between examiners of over 2 weeks, at 36 weeks the discrepancy represents about 1 week, whilst at 41 weeks of gestational age the difference represents less than 2 days.

(b) Occipito-frontal circumference (OFC)

Measurements of OFC by two examiners (E.J.D. and J.I.C.) on the same baby at different times of the day were subjected to statistical analysis. Each set of measurements of 16 babies was made in triplicate and the subsequent results were analysed by ANOVA. Table III 15 demonstrates that the doctor's interaction and residual mean square (MSq) are small in comparison to the subject MSq. Though the F value is significant, the difference in the mean value of the measurements between the two examiners is less than 0.2 mm. It is considered that such a difference is of minimal clinical importance.

(c) Crown-heel length (CH)

Measurements of CH on the same baby by J.I.C. and E.J.D. at different times on the same day in 6 cases were subjected to three factor ANOVA. The subject MSq is large when compared with all the other MSqs. Consideration of the interaction divisions shows absence of significance and it is therefore concluded that no serious error exists either in time or between examiners in the measurement of crown-heel length, see Table III 16.

(d) <u>Crown-rump length (CR)</u>

A comparison between examiners carrying out measurements on the same baby at different times of the day were made for 6 babies. The results were subjected to analysis of variance (ANOVA).

The mean square for doctors is higher than for subjects and therefore a highly significant F test is obtained (less than 1 per cent), see Table III 17. It is concluded that a serious error in crown-rump measurement exists between doctors. It is felt that the error arises from the difficulty in interpreting the size of the buttocks and the use of CR measurement is seriously limited by this difficulty.

(e) <u>Thoracic circumference</u>

Two separate examinations were made on the same day in 15 cases by each examiner. As Table III 18 shows, MSq for doctors compared with subject MSq was minimal. Thoracic circumference can be measured with a far greater degree of accuracy than was anticipated.

(f) <u>Caliper measurements of skinfold thickness (SFT)</u>

Each examiner made two separate measurements on the same day in 24 babies. Skinfold thickness was measured by the Verel and Kesterven forceps

(Verel and Kesterven, 1960). The results were subjected to ANOVA. As Table III 19 shows, the doctor and subject mean squares are of a similar magnitude and a serious error in the measurement of skinfold thickness exists when this type of caliper is used.

The measurement of neonatal skinfold thickness poses special problems. The use of the more accurate Harpenden Caliper - capable of measurement to 0.1 mm - requires the infant to remain still until the spring-loaded indicator comes to rest. The Verel and Kesterven caliper is not influenced by movement but is only capable of measurement to 0.6 mm (Farr, 1966). Skinfold calipers were therefore only utilised to quantitate the clinical impression (by palpation) of subcutaneous tissue loss and were shown to give a good correlation.

(ii) Clinical Progress of the Baby

(A) Clinical events

Details of clinical events were in the main recorded by the nursing and resident medical staff. Information on the occurrence of apnoeic attacks, infections, respiratory distress syndrome and other disease states and their subsequent management was obtained from the routine hospital notes and amplified if necessary by J.I.C. in discussion with hospital staff.

(B) Biochemical data

Measurements were made of biochemical changes that might have a damaging effect on the long-term development of the child. Those chosen were changes in the levels of blood glucose, bilirubin, and haemoglobin in the packed cell volume (pcv) of the blood.

(a) Blood glucose

During the first 72 hours, seven pre-feed values were obtained for LBW infants (at 10.30 a.m., 4.30 p.m. and 10.30 p.m.) and three from control infants (at 1 p.m.). The specimens of capillary blood were obtained by stabbing a warmed heel and immediately precipitated according to the method of Morley, Dawson and Marks (1968). As samples refrigerated for 72 hours showed no deterioration, analysis was carried out during the normal working week. In urgent clinical situations, Dextrostix were employed and confirmation of the result was made later by the reduction methods of Hoffman (1937).

Approximately one sixth of the samples were collected by E.J.D. and the comparative variation between the two observers and the laboratory staff was also not significant.

(b) Bilirubin

Serum bilirubin estimations were carried out when clinically necessary by the medical staff responsible for the general care of the nursery. All babies who are jaundiced have a routine bilirubin estimation on the fifth day of life. The measurement of the serum level was made in the routine hospital laboratory according to the method of O'Hagan et al (1957).

(c) Haemoglobin

Estimation of haemoglobin was carried out by an Evans Electroselenium (EEL) Haemoglobin Meter in accordance with the methods described by Dacie and Lewis (1970) based on the estimation of cyan-haemoglobin (Drabkin and Austin, 1932).

The measurement of haemoglobin is relatively inaccurate due to the small initial sample obtained (0.02 ml of blood), the deterioration of reagents and the lack of international standardisation. Due to the structure of the scale it is impossible to read levels of haemoglobin above 18 g and a further inaccuracy was introduced by diluting the final solution by 50 per cent.

(d) Packed cell volume was estimated on capillary blood in duplicate by the Hawksley Micro Haematocrit in accordance with the instruction manual. With a free-flowing capillary sample the error in measurement is 0.08 cm (1 S.D.) between two samples at the same time.

(5) Subsequent Follow-Up

Arrangements were made to follow up all the children at nine months of age to aseess the broad incidence of abnormal development. Of the total sample, 146 LBW infants and 146 controls attended for follow-up. Three experienced examiners were involved in the developmental examinations. Any sign of abnormality was an indication to refer the baby to the relevant clinic. A further attempt was made to assess the infants at four years of age by screening the Royal Aberdeen Children's Hospital records for the entire sample (this is the only children's hospital in the whole geographical area). The results obtained are likely to reflect with a reasonable degree of accuracy the rate of serious morbidity detectable up to the age of four years.

(6) Data Handling

The results were punched onto IBM cards and transferred onto magnetic computer tape to be analysed in an ICL system 4/50 computer. Cluster analysis was carried out according to Fortran H grouping (Veldman, 1967). The programme utilises a generalised distance function based on the concept of error sum of squares. Data processing and handling were under the direction of Mr. M. Samphier.

Conclusions

This chapter states the reasons for undertaking a study of low birth weight, the characteristics of the sample and the methodology of clinical, biochemical and data handling techniques.

CHAPTER IV

MATERNAL CONTRIBUTION TO LOW BIRTH WEIGHT

(1) Introduction

The maternal characteristics associated with impaired fetal growth range from biological factors, such as genetic constitution and height, through disease conditions, exemplified by pre-eclampsia and antepartum haemorrhage, to social attributes such as social class and illegitimacy. Since it is known that mothers of LBW infants deviate significantly in most characteristics from the normal population, the index cases and controls in the LBW study were matched for those maternal factors most likely to influence fetal growth. This made it possible to study in greater depth the matching characteristics chosen, namely social class, maternal height, smoking and pregnancy number. In addition the analysis was extended to embrace a wider range of items such as the identification of the mother who might deliver more than one LBW infant. As a result of this part of the study, it was hoped to calculate the extent of the adverse effect on fetal growth exerted by mothers of LBW infants when compared with a group of carefully matched controls. There are a number of factors which may have a very significant bearing on fetal growth - for example, maternal nutrition, illegitimacy and maternal anxiety - which were not measured in this study but which will be discussed later.

(2) Study of Maternal Characteristics affecting Fetal Growth

The purpose of this part of the study was to calculate the effects on fetal growth of maternal height, maternal height and weight in midpregnancy, smoking habits, pregnancy number and social class, in a carefully matched cohort of mothers of LBW infants and controls.

(i) Maternal Height

It is known that mothers of LBW infants tend on average to be shorter than the general population and standards are available for adjusting birth weight to allow for the effect of maternal height (Thomson, Billewicz and Hytten, 1968). Since maternal height was used as a controlling variable in this study, its basic effect on LBW could be demonstrated by calculating the adjustment for the controls, total LBW population, pre-term LBW and term LBW as shown in Tables IV 1 and IV 2. The calculations for pre-term infants are theoretical as the adjustment of birth weight was not available for this group in the original sample: for purposes of this theoretical exercise it is assumed that adjustments for maternal height apply equally to the birth weights of pre-term and term infants.

When birth weight was adjusted for maternal height (Tables IV 1 and IV 2) there was an increase over the mean for both LBW and control groups, which reflects the shorter stature of the mothers when compared with the general population (as the original work was based on the Aberdeen population (Thomson, Billewicz and Hytten), it can be assumed that a zero adjustment applied to the mother of average height). When the data were analysed by individual groups (Table IV 1), there was a significantly greater number ($p < 0.025$) of increased values amongst pre-term LBW (44/73), Table IV 1, than in the term LBW group (55/76), suggesting that mothers of term LBW infants are shorter. There was also a significant difference in the mean upward adjustment of birth weight between total LBW and controls ($p < 0.01$) and between term LBW and controls ($p < 0.02$).

It is concluded that the total numbers of LBW infants and controls where height adjustment has taken place do not differ significantly, as would be expected from the matching procedure. However, analysis of the mean weight adjustment does show a significant difference for LBW infants when compared with the controls (63.9 g SD 140.4 compared with 24.9 g SD 113.7 for controls). See Table IV 2.

(ii) Maternal Height and Mid-pregnancy Weight

A similar adjustment was carried out for the effects of maternal height and mid-pregnancy weight (MHMPW) on birth weight for total LBW, preterm LBW, term LBW and controls. Data were missing for 10 LBW infants and for 20 controls. Once again calculations for preterm infants are theoretical as corrections were not available. It was found that, where birth weight was adjusted for maternal height and mid-pregnancy weight there was a significant difference in the number of LBW infants with birth weights adjusted upwards compared with controls (Table IV 3). Of the total LBW group 98 birth weights were adjusted upwards for MH and MPW compared with 71 controls ($p < 0.001$). There was an equally significant difference ($p < 0.001$) in the number of term LBW infants (54/76) showing an upwards adjustment for MH and MPW compared with controls (71/149).

The mean birth weight adjustment upwards for maternal height and mid-pregnancy weight was also calculated (Table IV 4). The mean was 88.2 SD 164.9 for the total LBW cohort compared with 14.7 g SD 150.6 for the controls, a significant difference ($p < 0.001$). Though the mean birth weight adjustment for preterm LBW infants was significantly higher than for the controls ($p < 0.05$), the major contribution lies with the term LBW group, whose mean birth weight adjustment was even more significantly higher than the controls ($p < 0.001$). The results indicate that mothers of LBW infants, though of similar height to their matched controls, are significantly thinner.

It is concluded that maternal height and mid-pregnancy weight have a significant influence on fetal growth, which is evident even when maternal height is carefully controlled.

(iii) Smoking Habits

It is widely accepted that smoking has an adverse effect on birth weight. Lowe (1959) noted a reduction of 170 g in birth weight in a study of 2,042 pregnancies from six Birmingham hospitals. Herriott, Billewicz and Hytten (1962) found an average reduction of 160 g in a study of 2,745 Aberdeen births. Russell, Taylor and Maddison (1966) showed that the major reduction in birth weight occurred in babies delivered between 38 and 42 weeks and this was statistically significant ($p < 0.001$). It has been reported that maternal smoking during pregnancy impairs both head size and length (Davies, et al, 1976), though there must be some reservations about the validity of the findings; the differences in measurement were highly significant statistically, but they fell well within the error of measurements.

The effects of smoking during pregnancy are not confined to fetal growth, but have also been shown to influence the auditory component of neonatal behavioural tests (Saxton, 1977, personal communication). Babies of heavy smokers are quieter and generally less active when compared with controls from less heavy smokers. Of greater concern is the report of impaired reading, mathematics and general abilities at the age of 11 years (Butler and Goldstein, 1973). Part of this impairment may reflect increased absence from school due to excessive respiratory infection among the families of smokers.

There have been many theories as to why smoking has an adverse effect. Nicotine has been most often incriminated, though from the theoretical point of view its effects are extremely short-lived. Recently it has been postulated that the adverse effects of smoking are due to raised carbon monoxide levels. In a study of 222 women, Cole, Hawkins and Roberts (1972) noted significantly higher levels of carboxyhaemoglobin in the blood of smokers and this may in part explain the adverse effects of smoking. It has also been postulated that smoking depresses maternal nutrition, but this attractive hypothesis has not yet received any direct support.

It has been said by Yerushalmy (1972) that it is not the smoking, but the smoker, who is responsible for the impaired fetal growth, and his argument is based on the finding that women who subsequently became smokers had a high incidence of low birth weight infants prior to the time they smoked.

As maternal smoking or not smoking was a factor in matching controls in the present study, it was considered that the effects of smoking on birth weight might be demonstrated by comparing any differences in the amount smoked by mothers of the LBW infants and mothers of the control population. Data on smoking depend upon accurate recall by the mother, and this is particularly important when data are obtained after delivery. As information was collected on smoking habits during the pre-pregnancy period, the first 20 weeks and the second 20 weeks of pregnancy, the possibility of a changing pattern of tobacco consumption during pregnancy was analysed.

The smoking habits of the mothers of the LBW infants did not differ in any important respect from those of the general population of Aberdeen pregnant women during 1969-70. The results of the study show that, among mothers of LBW infants, there was a significant excess of heavy smokers in the pre-pregnancy phase ($p < 0.005$) and in the first 20 weeks of pregnancy ($p < 0.05$), but not during the last 20 weeks of pregnancy ($p < 0.1$), as shown in Table IV 5. The proportion of non-smokers remained relatively constant before and during pregnancy.

As pregnancy advanced, an increasing number of both LBW and control mothers became heavier smokers, but the difference in the rates of increase was not statistically significant. The changing pattern may have been due to increasing boredom with or anxiety about pregnancy or to better recall (since the information was collected after delivery).

Analysis of paternal smoking habits (Table IV 6) showed an excess of heavy smokers amongst fathers of LBW infants when compared with those of controls ($p < 0.01$). It seems most unlikely that the smoking habits of fathers could have any direct influence on fetal growth other than through social factors such as financial expenditure.

A detailed analysis of maternal and paternal smoking habits was carried out for preterm, term and growth retarded LBW infants and no significant differences between these groups were found. In summary, it has been shown that, despite careful matching of LBW and control infants, there was an excess of 5 per cent of heavy smokers amongst the mothers of LBW infants. It may be concluded that the contribution of heavy smoking to the impairment of fetal growth is of the order of 5 per cent.

(iv) Pregnancy number

Infants of first pregnancies are known to be lighter than those of subsequent births. In the present study, ordinal position in the family was selected as a matching variable because of its implications for sociological follow-up. There are fewer first pregnancies in the LBW group ($p < 0.05$) (see Table IV 7) than amongst the controls and this reflects the higher number of previous abortions in the LBW group. As second babies tend to be heavier than first, the LBW mothers in theory should have had a tendency towards heavier babies because of the excess of second pregnancies. However, this theoretical expectation is offset by a markedly poorer reproductive performance, in terms of both fetal growth and duration of pregnancy.

There are considerably less first pregnancies in the total LBW group (see Table IV 8) compared with controls ($p < 0.05$) but the excess of higher pregnancy number in LBW infants becomes more apparent and there is a statistical excess of third and fourth pregnancies in the total LBW group when compared with controls. The excess however lies predominantly in the preterm group (see Table IV 8).

(v) Social Class

Social class reflects numerous biological and social characteristics. The lower social class background of LBW infants has been documented in almost every study of the subject. Thomson, Billewicz and Hytten (1968) considered that, when all factors had been controlled, social class was probably responsible for a reduction of about 50 g in the birth weight of babies in Classes IV and V. The present cohort was matched in broad categories for social class according to the Registrar General's Classification of Occupation (General Register

Office, 1960) and the distribution is shown in Table IV 9. There was no statistically significant difference in the class distribution between total LBW and control infants or any of the sub-groups, implying accurate selection. It is true, of course, that the problems of matching for social class are less formidable than those of controlling for maternal height or smoking habits. Nevertheless, although the matching was reasonably satisfactory, it must be stressed that paternal occupation is a crude measure of the quality of the social environment. It should also be pointed out that the social class distribution of the LBW sample is heavily weighted towards social classes IV and V when compared with the distribution in the general population.

(3) The Contribution of Maternal Disease to Low Birth Weight

(i) Introduction

A history of maternal disease is commonly encountered among LBW infants, and indeed it may often be an aetiological factor in impaired or interrupted fetal growth. It is well known that disorder of pregnancy, such as severe pre-eclampsia, can cause intrauterine growth retardation (Baird, Thomson and Billewicz, 1957), or precipitate early delivery. However, the influence of other diseases, such as urinary tract infection, on pregnancy is more controversial, though Wren, 1969, has provided good evidence for its effect. In the present study, the effect of maternal disease on birth weight was examined from two aspects, viz, those conditions specifically associated with pregnancy such as toxaemia or pregnancy and antepartum haemorrhage and those diseases not specifically related to pregnancy. These latter included endocrine disorders, heart disease, anaemia, nervous and psychological disorders, gynaecological conditinns, diabetes, tuberculosis, urinary tract infection and miscellaneous infections; the tendency to abort is clearly an important concomitant of maternal disease but is not considered here.

(ii) Maternal disease associated with pregnancy

Amongst the total LBW population, compared with the controls, there was approximately a two-fold increase in the incidence of pre-eclampsia and hypertension ($p < 0.05$) and in haemorrhage before 28 weeks ($p < 0.025$), and a six-fold increase in other antepartum haemorrhage ($p < 0.001$): no significant differences existed between preterm and term LBW infants (Table IV 10). In all there were 108 separate recorded instances of maternal disease amongst mothers of LBW infants compared with 49 for the controls ($p < 0.001$), Table IV 10. The 108 instances occurred amongst 79 mothers of LBW infants and 45 controls ($p < 0.001$), see Table IV 12. In Table IV 12 it can be seen that the excess of mothers with diseases related to pregnancy in the LBW group was biased towards preterm infants (44), compared with term (35)($p < 0.05$). There appeared to be an excess of diseases associated with preterm IUGR (13/18) but the nnumber of cases was small.

(iii) Maternal disease not specifically related to pregnancy

Information concerning these conditions was obtained mainly from the antenatal record and is dependent to a considerable extent on maternal memory. In general, the incidence of disease amongst mothers of LBW infants is likely to be underestimated because of their poorer biosocial background and because of their later booking for hospital care.

The incidence of diseases not specifically related to pregnancy that might have a significant effect on outcome are listed in Table IV 11.

All the diseases recorded were then grouped under the one heading "Maternal disease unassociated with pregnancy" (Table IV 12). There is a slight excess of maternal disease amongst LBW infants (35) compared with controls (32), the excess amongst LBW infants being greatest in the preterm group, but neither excess reached statistical significance. The incidence amongst preterm IUGR infants was over 50 per cent, but not too much importance should be attached to this result as numbers were small.

Consideration of these mothers in each category with no recorded disease before or during pregnancy showed that the control mothers suffered less disease than the mothers of LBW infants. In all, 73 controls were without disease compared with 49 in the LBW group ($p < 0.005$): there were significantly fewer unaffected mothers in the preterm group (17) compared with the term group (32) of LBW infants ($p < 0.025$). The high rate of maternal disease amongst preterm IUGR infants has already been mentioned: only 3 out of 18 mothers has normal health before and during pregnancy.

(iv) Discussion

The role of maternal disease in causing low birth weight has been considered from two aspects - disease conditions associated with pregnancy and those than cannot be related directly to pregnancy.

Of the conditions specifically related to pregnancy, haemorrhage before 28 weeks indicates potential fetal difficulties whilst placenta praevia seems likely to be associated with early delivery. Toxaemia of pregnancy is relatively common, occurring in approximately 30 per cent of primigravidae and 15 per cent of subsequent pregnancies (MacGillivray, 1961). Pre-eclampsia may lead to acute therapeutic intervention and curtailed pregnancy; eclampsia and concealed accidental haemorrhage are relatively rare.

Consideration of the relative incidence of pregnancy disease amongst control and LBW infants (45/79) suggests that it is an important factor in the production of LBW. Thus there is an excess of 34 mothers (22.8 per cent) with pregnancy disease among the LBW group.

Disease conditions unrelated to pregnancy may be important but the relationship is not as striking as with pregnancy-associated disease. Maternal diabetes is known to be associated with preterm delivery and has been shown to cause a 23-fold increase in the incidence of respiratory distress, but a five-fold excess still remains when gestation is taken into account (Robert et al, 1976). Anaemia (Harrison and Ibeziako, 1973), and gynaecological conditions may be important antecedents of LBW but their effects are difficult to assess. In all 32 control mothers and 35 mothers of LBW infants had disease conditions unrelated to pregnancy, giving an excess of 3/149 (2.0 per cent) of conditions (Table IV 12) which is not a significant contribution to the production of low birth weight.

To calculate the contribution of all maternal disease to the production of LBW, the excess incidences of pregnancy and non-pregnancy diseases may be added together, a total of 24.8 per cent. It is unlikely that all these disease conditions are direct causes of LBW, but it seems reasonable to assume that at least half might play some role in its production. On this assumption it is postulated that maternal disease is an aetiological factor in some 12 per cent of LBW pregnancies.

(4) Maternal Nutrition during Pregnancy

The relationship of maternal nutrition to the syndrome of LBW has long been a subject of interest to workers concerned with fetal growth. In the light of recent reports of increased fetal weight achieved by dietary supplementation during pregnancy (Habicht, et al, 1974) and claims that maternal malnutrition may be a significant factor in the production of LBW, a review of the subject seems appropriate in a study of maternal factors influencing fetal growth.

Many experimental studies on the effects of impaired maternal nutrition in animals have created extreme situations of total or specific nutritional deprivation, such as are rarely, if ever, found in man. None the less some of these reports have important implications in the study of human fetal growth, for example the observation by Wallace (1945) that restricted feeding of sheep during the last 8 weeks of pregnancy reduced lamb weight by 40 per cent.

The effects of starvation on birth weight have been documented in three major studies (Antonov, 1947; Smith, 1947; Dean, 1951). Antonov (1947) reported the effects of starvation on conception and fetal growth during the seige of Leningrad. There was a profound drop in the conception rate and a significant fall in birth weight. Because starvation was prolonged and associated with the privations of war, the results from this Russian study are perhaps less valuable than Smith's (1947) report of the Dutch famine experience. The relatively short period of severe starvation inflicted in Holland on a previously well nourished population made it possible to show that starvation reduced the conception rate but birth weight was particularly reduced if severe caloric deprivation was operative during the last half of trimester of pregnancy. Dean (1951) in the MRC study in Wuppertal showed that the birth weight of the German population fell by 185 g after 1945, this being the time of maximum caloric deprivation, and then gradually rose to its pre-war level by 1948. The evidence appears convincing that poor nutrition has a significant effect on birth weight but it is pertinent to stress that malnutrition is only one of many factors operative in wartime. Further information about the possible effects of malnutrition during pregnancy has been obtained from stillbirth and early neonatal mortality rates. During World War II there was a significant reduction in the perinatal mortality rates in the United Kingdom and this was thought to be due to the elimination of the grosser forms of poverty together with an assured supply of nourishing and cheap food for pregnant women (Duncan, Baird and Thomson, 1952). Further epidemiological evidence has been presented by Bergner and Susser (1970) suggesting that perinatal mortality rate among American negroes in New York might fall from 44 per thousand to 26 per thousand (the figure for the white population based on 1958 to 1961 data) if the mean birth weight were increased by 200 g, and attributing such a potential increase to the effects of improved nutrition. It would require a carefully controlled prospective study to test this hypothesis.

With high rates of neonatal survival already achieved in many communities, there has been an increasing tendency to use the quality of survivors as the yardstick of medical care. There are many reports on the long-term outlook for children with severe malnutrition - for example, kwashiorkor - which demonstrates striking impairment of intelligence in affected children when compared with controls. The major defect of all these studies is the impossibility of matching a family whose poverty or social incompetence allows the development of such extremes of malnutrition. In a follow-up study of the mental development of 19 children treated between 1½ and 3 years of age for malnutrition (Champakam, Srikantia and Gopalan, 1968), the closest attention was paid to matching which included age, sex, religion, caste, family size, educational background of parents, locality of residence and class in school. The study demonstrated a significant reduction in IQ amongst the malnourished group compared with the controls. However, the authors point out that the uncontrolled factors of parental motivation and responsiveness may be all-important in determining the development of malnutrition in these children.

There is only one satisfactory long-term study of the sequelae of maternal starvation during pregnancy. In a follow-up of the Dutch famine cohort, Stein (1975) demonstrated that malnutrition during pregnancy had no effect on tests of mental performance at the age of 18, when military draftees were compared with matched controls.

There is increasing evidence from autopsy studies that newborn infants of malnourished mothers have similar characteristics to infants and young children succumbing to postnatal malnutrition. Naeye (1965) reported that 11 newborn infants with birth weights below -2 standard deviations from the mean had similar post mortem body weight ratios to those of 7 malnourished infants. These studies were further extended to autopsy examination of organ and cell structure of infants born to impoverished mothers - assuming poor nutrition - when compared with infants of mothers with incomes above the poverty line. A cohort of 1002 consecutive autopsies was analysed: after excluding those cases with an aetiology known to influence fetal growth - for example, toxaemia of pregnancy and congenital abnormalities - and cases where financial information about the parents was lacking, 469 autopsies remained for further study. In the 83 cases defined as "poor" it was found that the birth weight was reduced by up to 18 per cent, length and organ size were smaller and subcutaneous fat was significantly less. When considering maternal factors that might have influenced fetal growth, it was shown that the "poor" mothers were not significantly different in height and age from the 386 mothers defined as from "non-poor" backgrounds (Naeye, et al, 1971). If poor maternal nutrition is indeed a significant aetiological factor in LBW, correcting deficient diets during pregnancy might be a major advance in perinatal care.

A number of studies report the effects of maternal dietary supplementation on birth weight: the work of Habicht, et al,(1974) seems the least affected by methodological difficulties. As the influence of maternal nutrition on birth weight is probably small (200 g) it would be important to study a group of mothers delivering infants with weights around 2.5 kg rather than 3.5 kg. Habicht and his colleagues have described the effects of dietary supplementation in 288 Guatemalan women living under very poor rural circumstances: they found that pregnant women ingesting an additional 20,000 calories during the whole pregnancy had infants with a mean birth weight of 3.22 kg compared with 2.98 kg for babies of women ingesting only an additional 5,000 calories. The additional consumption of 20,000 calories over a 20 week period during pregnancy is approximately equivalent to 2 slices of pan bread, 1 packet of potato crisps or 1/3 of a pint of milk per day, a relatively small amount to the average over-nourished European!

Factors influencing birth weight, such as maternal height, were similar in each of Habicht's groups. In a study of 452 mothers, Thomson (1959) concluded that maternal weight was much more important in determining birth weight than the caloric value of maternal diet. While this conclusion may be valid for babies with birth weight around 3.5 kg, quite a different picture may emerge when babies with birth weight in the region of 2.5 kg are studied and indeed this may be the nub of the debate on maternal nutrition in relation to pregnancy.

Conclusion The subject of maternal nutrition and its importance to the fetus has been an area of continuing interest. There is a wealth of reports of animal experiments showing increased fetal wastage, impaired growth and learning and behavioural deficits in the young of malnourished mothers. Unfortunately, these experiments have often been extreme and cannot for ethical reasons be repeated in the human. There are a number of reports of impaired fetal growth following maternal starvation in exceptional situations. However, the suggestion that learning deficits in childhood may be sequelae can only be inferred from studies of infants and children with postnatal malnutrition such as kwashiorkor. It would seem from animal work that maternal malnutrition during pregnancy can affect behaviour and learning during childhood but against this must be set the report of the only long-term controlled study of starvation during pregnancy which failed to show any effect on the intelligence of 18 year old males (Stein et al, 1975). Recent reports of the favourable influence of dietary supplementation on birth weight are of particular importance when viewed in the light of epidemiological data suggesting that a small increase in birth weight amongst infants weighing around 2.5 kg might have a significant impact on perinatal mortality. The implications for this study seem to be the possible identification of a further aetiological group, namely, that caused by maternal malnutrition during pregnancy.

(5) Illegitimacy

The adverse effects of illegitimacy on pregnancy and subsequent outcome are well documented. Mothers of illegitimate babies tend to be younger, with a five-fold excess of very young mothers when compared with their married peers (Crellin, Pringle and West, 1971). In the past, illegitimacy has tended to be associated with unskilled, unattractive menial occupations (Thompson, 1956), but the pattern has been altering in recent years and may reflect a change in attitude towards sexuality in general (Illsley and Gill, 1968). The incidence of diseases associated with pregnancy appears to be higher. The general disadvantage that an unmarried mother faces is reflected by a two-fold increase in the fetal and neonatal mortality rate (Schneider, 1968). Twice as many illegitimately born infants fall into the low birth weight category (Schneider, 1968) and there is a 157 g reduction in the mean birth weight which is reflected in the slightly higher incidence of IUGR, i.e. 12 per cent of illegitimate infants below the 10th centile and 19 per cent with birth weights above the 75th centile (Crellin, Pringle and West, 1971). The frequency of IUGR is not as high as might be anticipated from the reduction in mean birth weight, but this may be partially due to an excess of preterm babies influencing the mean birth weight. Single mothers tend to deliver an excess of pre and post-term infants (Crellin, Pringle and West, 1971).

There is abundant evidence that illegitimacy influences fetal growth. The subject has considerable socio-biological importance but the complexity of the relationship renders detailed analysis extremely difficult and further study is unlikely to add significantly to our understanding of the maternal factors which influence fetal growth.

(6) Psychosocial Factors in the Genesis of Low Weight at Birth

It is generally considered that in over half of all infants admitted to hospital because of failure to thrive, maternal deprivation or adverse social conditions account for their poor progress. Clinicians experienced in the care of children find no difficulty in accepting the central role of psychosocial factors but scientific proof is hard to obtain. Data from animal work broadly support this thesis and Joffe (1969) concluded that despite the differences in procedure from one study to another, it seems reasonable to conclude in animals, that the procedure of prenatal stressing increases the emotional state of the offspring, though the direction of the effect is to a large extent dependent upon the strain of the subjects. Evidence from human studies is less convincing and Joffe (1969) himself was doubtful about the effects of emotional events in pregnancy on subsequent fetal development. Such evidence as there is provides rather tenuous support for the theory that maternal emotions can modify fetal growth.

Rejection of the fetus by the mother may be a very complex phenomenon involving not only emotional stress, but also impaired nutrition, disturbance of sleep and a variety of social factors. Indirect evidence of rejection comes from the report that among 14 unmarried black mothers of infants suffering the effects of severe fetal malnutrition, 5 submitted their babies for adoption, as compared to none of 58 mothers of wellnourished infants ($p < 0.001$) (Miller and Hassanein, 1973). Sontag (1966) has presented the most convincing evidence that maternal reaction may influence the fetus. In 8 mothers undergoing extremes of anxiety, fear and grief, excessive fetal activity was recorded by direct methods.

There is thus some evidence that maternal emotional factors are related to fetal activity, and it can be postulated that maternal rejection of the fetus may result in a reduced rate of fetal growth. However, with the paucity of methods available for determining fetal growth and assessing the effects of noxious agents on the fetus, it seems unlikely that much headway will be made in the near future in elucidating the role of emotional stress in the genesis of low weight at birth.

Conclusions

This chapter assesses the maternal contribution to low birth weight by analysing a number of maternal characteristics. These comprise height, maternal height related to midpregnancy weight, smoking habits, pregnancy number and social class. Maternal disease, nutrition during pregnancy, illegitimacy and psychosocial factors are also discussed. It is concluded that mothers of low birth weight infants are biosocially inferior to their matched controls.

CHAPTER V

INTRAUTERINE GROWTH RETARDATION

(1) Definition of Intrauterine Growth Retardation

The definition of intrauterine growth retardation (IUGR) has presented many problems in the past because of the multifactorial nature of the process. Controversy still rages as to the most appropriate definition, but in practice the most widely used criterion is weight for gestational age. Most workers employ values falling below the 10th centile but others use more stringent criteria of below the 5th centile or even below -2 standard deviations.

However, the use of birth weight for gestational age may not be the most sensitive method, indeed, from theoretical considerations, head circumference is more appropriate. In this section, a brief comparison will be made of nine different clinical methods of defining IUGR.

(i) Use of Weight for Gestational Age Charts

Impaired intrauterine growth (IUGR) has been defined in a variety of ways, most frequently by the use of weight for gestational age charts, e.g. Streeter (1920); Gruenwald and Minh (1961); Lubchenco et al (1963). Other methods have included the use of clinical features such as wasting and cracking of the skin (Clifford, 1957); Sjostedt, Engelson and Rooth, 1958); the ponderal index (Lubchenco, Hansman and Boyd, 1966); the percentage weight loss in comparison to the mean weight (Scott and Usher, 1966); and the discrepancy from sibling weight (Turner, 1971).

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However, the use of birth weight for gestational age may not be the most sensitive method, indeed, from theoretical considerations, head circumference is more appropriate. In this section, a brief comparison will be made of eight different clinical methods of defining IUGR.

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The use of weight for gestation standards has evolved as the basic way of measuring fetal growth, but two difficulties arise with the use of centile charts. Firstly, the inaccuracies of gestational age, a problem common to all methods of assessing impaired fetal growth; secondly, the concealment of the heterogeneous nature of IUGR by the statistical approach. It should be possible to measure IUGR by the clinical features of the infant; these are readily described at term, but less easily before 36 weeks. The concept of dysmaturity is widely used, but it is ill-defined and subject to wide variation from centre to centre.

The earliest anthropometric study was carried out by Clarke (1786), who measured the birth weight of 120 newborn infants. The first study widely used in clinical practice is that of Streeter (1920) from the Carnegie collection. The mean birth weights of 704 embryos and fetuses up to 28 weeks were combined with data compiled by Meyer (1915) on 2394 infants born in the John Hopkins Hospital. The results were expressed as mean, maximum and minimum birth weights as well as in graphic form. Later workers employing these data have usually arbitrarily selected a percentage below the mean as their criterion of growth retardation e.g.(Scott and Usher, 1966).

A number of authors have subsequently published weight for gestational age standards, more recent papers being based on centile rather than standard deviation charts. As birth weight is non-gaussian in distribution, standard deviations are not applicable, though this statistical approach has allowed certain authors, e.g. Usher and

McLean (1969) to create standards based on a very small population. Gruenwald and Minh (1961) published weight for gestational age tables expressed as means and standard deviations based on surviving infants and autopsies, the latter being derived from several different hospitals. The large number of autopsies in the series inevitably influenced the results but nonetheless the data are of some value as indices of growth in an abnormal population. Shortly after this report, Lubchenco et al (1963) published the definitive work in this area of research. Birth weight data were collected on 5,635 liveborn infants, admitted to Colorado General Hospital and centile distribution tables were calculated. The mean birth weight at each gestational age appears to be lower than in other studies, which probably reflects a combination of the effects of altitude and the exclusion of gross pathological conditions which might influence birth weight such as hydrops, anencephaly and maternal diabetes. It seems likely that the socio-economic characteristics of this hospital population were not representative of the general population and this may also account for the lower mean birth weight.

Since the Denver report, standards for fetal growth have been published on a wide variety of populations throughout the world. Of all the studies to date, the report of Thomson, Billewicz and Hytten (1968) is the best. It was based on 52,004 legitimate single births in the city of Aberdeen from 1948 to 1964. The results were expressed in centiles from the 5th to the 95th: corrections to the birth weight for sex of the infant, pregnancy number, maternal height and mid-pregnancy weight are available, making these tables the most sensitive over the range of gestational age considered. Unfortunately values were not calculated before 32 weeks of pregnancy because of the small number of patients available for study at this short gestation. However, it must be pointed out that lack of numbers has not inhibited other authors from reporting values for short gestation. For example only 300 infants were studied over the whole range of gestation (25-44 weeks) by Usher and McLean (1969): as a consequence of this limitation in numbers, the results had to be expressed as standard deviations rather than centiles (the problems created by this type of statistical analysis will be dealt with in a later section).

The study by Kitchen (1968) of a Melbourne Hospital population of 2,637 patients of Anglo-Saxon, Italian and Greek origin is one of the few expressing results in both centiles and standard deviations. Data derived from hospital are less satisfactory than those from geographical populations, but they are useful in establishing standards in communities with a large migrant population and represent a first step towards the creation of fetal growth standards for different ethnic groups.

Perhaps the largest cohort is recorded in a study of the total population of Norway by Bjerkedal, Bakketeig and Lehmann (1973). Birth weight by gestational age was reported by centiles for 125,485 births from 25 to 48 weeks. Some reservation must be expressed about the data earlier than 34 weeks, because a number of babies of very heavy birth weight were included; at the opposite extreme, gestational ages over 45 weeks were also reported, an unusual finding in modern obstetric practice.

There are clearly a number of snags in the use of weight for gestation charts as the basis for defining fetal growth. Nevertheless, a wide variety of such standards is now available for classifying the relative growth of babies. Their value is unquestioned but it is important to be aware of their limitations.

(ii) Comparison of Centile Distribution of Birth Weight, Occipito-Frontal Circumference, Crown-Heel Length, Ponderal Index and Maternal Height Adjustment

(A) Method

Centile distributions for birth weight (Lubechnco et al, 1963), occipito-frontal circumference (OFC), crown-heel length and ponderal index were classified according to Lubchenco, Hansman and Boyd (1966). Centile distributions for birth weight, maternal height and mid-pregnancy weight adjustment, and gestational age derived from the total maturity score, were classified according to the data of Thomson, Billewicz and Hytten (1968).

The centile distribution of each anthropometric measurement (birth weight, OFC, crown-heel length and ponderal index and adjustment for maternal stature) was plotted for controls, total LBW, preterm LBW and term LBW infants and is shown in Graphs 1 to 4.

(B) Controls

The population distributions by centile for the controls were similar whether weight for gestation was defined according to the data of Lubchenco et al or of Thomson et al, or was adjusted for maternal stature. They were also broadly similar for the parameters not involving weight, namely OFC, crown-heel length, and ponderal index, though the general trends of the latter were not in such close agreement (Graph V 1).

(C) Total Low Birth Weight

A similar graph was drawn for the centile distribution of each anthropometric measurement for the total LBW population. Graph V 2 shows that the centile distribution for weight is very similar whatever method of definition is used, but is very different for OFC, crown-heel length and ponderal index. Such a finding might be anticipated since weight was the criterion of selection for this study because of its ready availability and use in previous studies. From theoretical considerations, head growth might be more important as an indicator of long-term development and if selection had been based on head circumference falling below the 10th centile, a different population could easily have been obtained.

(D) Preterm Low Birth Weight

When a similar graph was drawn for preterm LBW infants (Graph V 3) there was broad overall agreement for the centile distribution for each anthropometric parameter, with the exception of the ponderal index and gestational age derived from the total maturity score. The lack of agreement for the total maturity score is quite striking and suggests a degree of inaccuracy in calculating the date of the last menstrual period. The population distribution by ponderal index tends towards the mean and might imply that despite the low birth weight of many preterm infants, they are relatively well-nourished for their length.

(E) Term Low Birth Weight

A similar analysis was carried out for term LBW infants (Graph V 4). It might be anticipated that 80 per cent of the term LBW infants would fall below the 10th centile when weight was used as the criterion of growth. When the centile distribution for OFC, crown-heel length and ponderal index are drawn on a graph, a totally different pattern emerges. Over half the population are above the 25th centile for OFC and crown-heel length and above the 50th centile for ponderal index.

The graphs clearly demonstrate that in the population of controls, the distribution of low centile position is approximately similar for all the anthropometric measurements. When a similar analysis is carried out for LBW infants, a different pattern emerges, due to the selection of sample by weight. However, it may be that a low centile position in other anthropometric measurements is a better parameter for detecting impaired fetal growth, and this proposition will be examined in the next section.

(iii) Definition by Statistical Analysis of the Various Anthropometric Methods

(A) Methodology

A statistical comparison was made of the centile distribution for the various anthropometric methods of defining fetal growth. The centile distribution of the population was defined according to the data of Lubchenco and Thomson was analysed by matrix analysis for total LBW, preterm LBW and term LBW infants and for controls. Comparisons are possible between anthropometric measurements when the original standards have been derived from the same population, e.g. Lubchenco et al's data for body weight, head circumference, crown-heel and ponderal index. Similarly, birth weight, maternal stature and adjustment for gestational age (derived from total maturity score) could be analysed on the charts based on Thomson's data. Comparisons were not made between data obtained by the methods of Lubchenco and of Thomson, because the original observations were made on two very different populations.

(B) Results

The results showed that controls are significantly different in centile distribution for birth weight against head circumference and crown-heel length against head circumference, but not for any of the other anthropometric measurements (Table V 1). Amongst the controls, head circumference seems to have a different population distribution. There was no variation between ponderal index and the other anthropometric measurements (Table V 1). These differences probably reflect the birth weight selection of the sample.

In the whole low birth weight group, birth weight and ponderal index differed significantly between themselves, and in addition both showed significant differences from all other anthropometric measurements (Table V 2). The results probably reflect the selection effect of birth weight upon the sample.

Among preterm LBW infants the only significantly different result was found between length and ponderal index (Table V 3). The same statistical analyses were carried out for term LBW infants and once again birth weight shows a significant correlation with head circumference, crown-heel length and ponderal index (Table V 4). There also appeared to be a statistical relationship between head circumference, ponderal index and crown-heel measurement ($p < 0.005$).

(iv) Use of a Percentage Reduction in the Mean Birth Weight

The selection of an arbitrary percentage reduction in the mean birth weight has been used as a basis for defining growth retardation. Theoretically, it seems a simple and useful method of solving the vexed question of defining IUGR. Scott and Usher (1966) suggested a 15 per cent reduction in the mean birth weight for gestational age, based on the values defined by Streeter (1920), as the definition of mild IUGR and a 25 per cent reduction as the criterion of severe IUGR. Fitzhardinge and Steven (1972) used a 30 per cent reduction according to Streeter's curves in defining IUGR in term LBW infants. Drillien (1972), in a sample of 283 infants below 2001 g birth weight, defined a group of very small-for-dates infants with a birth weight falling 40 per cent below the mean when compared with the Denver standards.

This method has the obvious attractions of simplicity and practicality, but examination of fetal growth charts indicates major problems. Study of Usher and McLean's fetal growth tables confirms that for their population, -2 standard deviations coincides with a 25 per cent reduction in the mean birth weight at all gestational ages (Graph V 5). However, this may be due to the small size of their sample (300 babies) and examination of other fetal growth charts shows major difficulties.

Analysing a considerably larger sample, it was found that -2 standard deviations from the mean represented a reduction in weight considerably in excess of 40 per cent for infants delivered before 34 weeks, falling thereafter to 26 per cent at term (Gruenwald and Minh, 1961).

Similar analyses were carried out for the 10th centile using the data of Bjerkedal, Bakketeig and Lehmann (1973), Lubchenco et al (1963) and Thomson, Billewicz and Hytten (1968). Of infants delivered before 28 weeks in Lubchenco's study, those at the 10th centile weighed 25 per cent less than the mean compared with 18 per cent at 40 weeks (Graph V 6). A similar analysis of Bjerdedal and Thomson's data showed that the mean weight for infants at the 10th centile delivered at 32 weeks of gestation was approximately 26 per cent below the mean weight for gestational age and at 40 weeks was 16 per cent. When a similar analysis was carried out for the 5th centile, there was a 30 per cent reduction at 33 weeks, compared with 20 per cent at term.

It is concluded that this method of defining IUGR is not valid throughout gestation. For it to be effective, different arbitrary percentages would have to be applied at 28 weeks and 40 weeks, and such a mathematical approach has no advantages.

(v) Use of Anthropometric Ratios - Ponderal Index and OFC/Length

(A) Ponderal Index

(a) Introduction

In the early days of the study of fetal growth it was often hoped that either a simple mathematical formula or combination of measurements would describe fetal growth. Many of the attempts have been intriguing mathematical exercises and Roberts (1906) argued that fetal growth (after the third month) was related to time divided by constant, as shown in the formula

$$\text{Weight} = \frac{(\text{months})^3}{104}$$

Jackson (1909) in a study of 43 embryos and fetuses found that fetal growth took place at a fairly regular rate and was related to age in days 4 divided by constant, as shown

$$\text{Weight(g)} = \frac{\text{Age (days)}^4}{37}$$

Tuttle (1908) showed that the weight of the fetus appeared to have a good relationship to the square of the gestational age minus 2, as shown

$$\text{Weight} = 100\,\frac{(\text{months} - 2)^2}{2}$$

Though these combinations involving gestational age were interesting, their use was limited due to the idiosyncrasies inherent in the reporting of gestational age.

The most useful ratio of anthropometric measurements reported to date has been described by Rohrer (1908). Rohrer's ponderal index is the ratio of weight divided by crown-heel length^3.

$$\text{Ponderal Index} = \frac{\text{Weight}}{(\text{Crown-Heel})^3}$$

More recently the ratio of length ÷ occipito-frontal circumference was found to give a constant and has been used by Miller and Hassanein (1971).

Interest in Rohrer's index (PI) has fluctuated but has more recently been revived by the report of Lubchenco, Hansman and Boyd (1966) who described the centile distribution for this index. Further impetus to the use of this ratio has been the report of Miller and Hassanein (1971) who assessed its value in the diagnosis of impaired fetal growth. In 33 clinically malnourished infants with PI below the 3rd centile there was an excess of poor maternal weight gain, PET, major chronic illness and illegitimacy. (Miller and Hassanein, 1973) Recently it has been speculated that the effects of maternal malnutrition as evidenced by poor weight gain might be recognised in the fetus by a low PI index (Miller and Hassanein, 1974).

It seemed that more detailed examination of the ponderal index might be fruitful in the analysis of fetal growth and with this in mind the PI was analysed in its relation to the LBW study.

(b) Methodology

The ponderal index of each patient was calculated according to Rohrer (1908) and the relative centile position for this ratio was obtained from the tables of Lubchenco, Hansman and Boyd (1966).

(c) Results

The distribution of ponderal index by LBW and control infants is shown in the table (Table V 5). Low birth weight infants have a lower mean value because of their association with short gestation and IUGR. The distribution of values among preterm, term and control infants, ≤ 2.3 and ≥ 2.6, shows the expected excess of low values, there being only six controls with a PI ≤ 2.3.

The incidence of maternal and neonatal disease were very similar by broad PI groups. When a similar analysis for term LBW for low PI (below 2.3) compared with high PI (above 2.6) was made for a variety of clinical characteristics, some significant differences were found. Plantar skin creases were more wrinkled at low PI amongst term LBW compared with high values ($p < 0.025$). There was a greater tibial skin loss in term LBW of low PI ($p < 0.005$) and more evidence of drying and cracking on the skin of the hand ($p < 0.005$).

(d) Conclusions

The use of PI as a definition of fetal growth does not show the promise that some workers have assumed from theoretical considerations. The value of the PI in identifying populations with an excess of problems was carried out.

(B) Ratio of Occipito-Frontal Circumference to Crown-Heel Length

(a) It was hoped to identify an anthropometric ratio which might define impaired fetal growth which would dispense with the use of gestational age. In all, some 25 anthropometric ratios were studied in the course of this thesis and all but two were rejected because of their variability and inconsistency. Along with the ponderal index, the ratio of head size to crown-heel length maintains a constant ratio between 0.67 and 0.75. High values reflect a relatively greater head growth to body length or short body length, and conversely low values represent either a small head or an increased relative body length. A broadly similar ratio, i.e. crown-heel to occipito-frontal circumference was utilised by Miller and Hassanein (1971) when a large cohort of over 1437 babies were studied and four groups of abnormal patterns of fetal growth were identified, i.e. short crown-heel length; disproportionate growth between body length and head size; babies who were malnourished due to lack of deposition or excessive depletion of soft tissue mass and a group with excessive accumulation of body fat. Unfortunately only illustrative examples of disorders of fetal growth were given rather than any detailed statistical analysis. In a further study, Miller, Hassanein and Hensleigh (1976) felt that short crown-heel length for gestation was more commonly found amongst mothers who smoked.

A broadly similar analysis was carried out in the low birth weight study, namely the ratio of occipito-frontal circumference to crown-heel, firstly to determine the overall distribution in the low birth weight population of the ratio, and secondly to assess its value in reflecting both abnormal obstetric and neonatal problems and hopefully to identify abnormal patterns of fetal growth. The ratio was analysed for its relation to gestation and centile distribution as well as to maternal and neonatal clinical details.

(b) Results

The distribution of the ratio of head circumference to crown-heel length is shown in Table V 6 and values for controls, total preterm and term low birth weight babies was found to be very similar. The controls had a slightly lower mean (0.70) compared with the other groups (0.71) but this was not statistically significant.

Gestation: The relationship of the ratio to gestation was examined and as gestation proceeds from 28 to 35 weeks a very slight rise in the occipito-frontal circumference/

crown-heel ratio takes place, but this is not significant, as demonstrated by a correlation coefficient.

Centile position: The relationship of the OFC/CH to centile position was studied and high ratios - i.e. a large OFC compared with length - was noted for preterm LBW infants. A marginally-similar result was found in term low birth weight infants.

Neonatal and maternal morbidity patterns: A detailed study was carried out and abnormalities of the OFC/CH ratio were not related to a significant increase in maternal or neonatal morbidity patterns.

(c) Analysis of Patients with Extremes of OFC/CH Ratio (below or equal to 0.67, and above or equal to 0.74)

Extremes of OFC/CH ratio might reflect significant abnormalities of fetal growth and a more detailed analysis was carried out. Twenty-one low birth weight infants and 25 controls were identified with values equal to or below 0.67 and above or equal to 0.74. More detailed analysis of those babies with ratios falling outwith the extremes, either by combining those with values ≤ 0.67 and ≥ 0.74, or using each definition separately, failed to reveal an excess of widely divergent anthropometric measurements such as an excessively long crown-heel length.

(d) Maternal Smoking

The smoking habits of the mothers of these infants were examined and no statistical association with extremes of OFC/CH ratios were found. Miller, Hassanein and Hensleigh (1976) suggested that short crown-heel length for gestation was associated with maternal smoking. Though the use of anthropometric ratios is not strictly comparable, wide discrepancies of relative growth detected by the OFC/CH ratio did not support their finding.

A further analysis relating maternal smoking patterns to low centile position ($<$ 10th) for birth weight, crown-heel length and occipito-frontal circumference was carried out. As might be anticipated, there was a low incidence of non-smokers (32.3 per cent for low birth weight and 35.7 per cent for controls) amongst mothers with birth weights below the 10th centile. There was an almost identical incidence for a crown-heel length below the 10th centile (36.1 per cent) amongst low birth weight infants compared with their controls. However, occipito-frontal circumference did not seem to be influenced by maternal smoking patterns, as 52.2 per cent of mothers of low birth weight infants with centiles below the 10th centile for occipito-frontal circumference did not smoke.

(e) Maternal Height

Maternal height did not appear to be related to extremes of the OFC/CH ratio. In control infants with ratios ≤ 0.67 (i.e. relatively long), mean maternal height was 156.7 cm SD 5.5, compared with 155.0 SD 4.0 for those with ratios ≥ 0.74 (short length). In the LBW with low ratios ≤ 0.67, mean maternal height was 158.0 SD 9.27, compared with 155.1 SD 6.9 for ratios ≥ 0.74. There was no statistically significant difference between these results. The major potential advantage of the use of these ratios is the avoidance of using gestation as a variable. Unfortunately the OFC/CH ratio does not appear to have been a very useful parameter for defining abnormalities of fetal growth.

(2) Classification of Growth by Comparing the Relative Centile Positions of Occipito-Frontal Circumference, Birth Weight and Crown-Heel Length

(i) Introduction

An attempt was made to distinguish different patterns of fetal growth on a theoretical basis by comparing the relative centile positinns for occipito-frontal circumference (OFC), birth weight (BW) and crown-heel length (CH) in the same baby. If two of these measurements were at the same centile position, then the third was assumed to describe the pattern of fetal growth, e.g. OFC and CH on the 50th centile and BW on the 10th centile, the infant being described as "thin". A major difficulty with this approach related to infants where all three centile positions differ. In this situation an arbitrary decision was taken and where the centile position of all three characteristics differed, that with the lowest centile position was taken as the descriptive characteristic. Centile position was arbitrarily divided into groups of < 10, $10 \leq 24$, $25 \leq 49$, $50 \leq 74$, $75 \leq 90$.

The different patterns of growth were classified as follows:

Birth weight centile lower, defined as thin.

Birth weight centile higher, defined as fat.

Head circumference lower, defined as small head.

Head circumference higher, defined as big head.

Crown-heel centile lower, defined as short.

Crown-heel centile higher, defined as tall.

Where all three characteristics differ the lowest centile position was taken.

Utilising the tables of Lubchenco et al (1963), and Lubchenco, Hansman and Boyd (1966) the centile position of each index and control infant was calculated for BW, OFC, and CH. The cohort was divided into preterm, term, total birth weight and controls.

(ii) Patterns of Growth by a Divergence of at least one Centile Position

When comparing controls with the total LBW group (Table V 7) there are significantly more "short" control infants (37 compared with 14: $p < 0.001$) and fewer "thin" controls (22 to 36: $p < 0.05$), Table V 8. The excess of "short" infants may possibly reflect the genetic influence of mothers of low stature: however, the distribution of maternal height amongst the controls defined as "short" was similar to that in the control population and the mean weight adjustment for height of mothers of "short" babies was + 14.9 g, compared with + 24.9 g for the control population.

When comparing the preterm group with the controls, there were fewer preterm infants defined as "bigheaded" ($p < 0.05$) and an excess of "fat" infants ($p < 0.025$) compared with controls (Table V 9), but the remaining categories were equally distributed. When term LBW infants were compared with controls (Table V 10) there was a relative increase in those defined as "thin" ($p < 0.001$) but not with "bigheaded" category ($p < 0.1$): in addition there was a deficiency of "short" infants ($p < 0.001$). Those defined as "fat" and "small-headed" did not show a significant difference, but this was to be anticipated in view of the way the sample was selected. When the preterm infants are compared with the term group there is a statistical excess amongst preterm babies of "short" (13 of 73 against 1 of 76: $p < 0.001$), "fat" (12 of 73 against 1 of 76: $p < 0.005$), and "small-headed" (11 of 73 compared with 1 of 76: $p < 0.01$). There was a considerable excess amongst term infants of "thin" (26 of 76 compared with preterm 10 of 73: $p < 0.005$) and "bigheaded" (22 of 76 compared with 6 of 73: $p < 0.005$) (see Table V 11).

Amongst term LBW infants there was an excess of "thin" and a deficiency of "short" infants; amongst preterm, there was an excess of "fat" and "small-headed" and a deficiency of "short".

(iii) The Incidence of Clinical and Morbidity Characteristics by Relative Centile Position for Preterm, Term and Control Infants

(A) Preterm LBW

In this section a study was made of the various clinical characteristics according to their relative centile position and the clinical and morbidity patterns were compared against the group defined as "appropriate" for gestation. Amongst the group defined as "short", there was a deficiency of fetal distress, an excess of low scores for tibial skinfold thickness, and an excess of mothers of short stature. In "fat" infants, there was an excess of maternal disease and of low scores for tibial skinfold thickness. In "thin" infants, there was a dearth of females and a history of abortions, but an excess of PET, minimal dehydration and tibial subcutaneous tissue loss. In the "bigheaded" group there were reduced rates of abortion and PET and fewer female infants; this pattern was reversed in the "small" group. These results indicated trends and none of the findings reached statistical significance, because of the small numbers involved.

(B) Term LBW Infants

A similar analysis was carried out of the neonatal and maternal morbidity patterns for the various groups of term LBW infants. From the initial analysis a number of trends were evident but failed to reach statistical significance. For those term LBW infants defined as "long", the abortion rate appeared higher, as well as the prepregnancy smoking patterns. Amongst those defined as "thin" the incidence of PET and tibial skinfold loss was high and the minor abnormality rate was low. For "bigheaded" infants, the abortion rate was low, but the fetal distress rate, tibial skinfold loss and incidence of minimal dehydration were high. The only item shown to be statistically significant ($p < 0.05$) was the high rate of minor abnormalities in those infants defined as "appropriate for gestational age" when compared with infants defined as "bigheaded" and "thin".

(C) Control Infants

A similar analysis was carried out for control infants where a classification of fetal growth was carried out by relative centile position. Significan differences were found between the "appropriate" and "long" groups for minor abnormalities ($p < 0.01$), and for social class when comparing "appropriate" with those defined as "short".

A number of trends were noted for tibial skinfold thickness amongst the "fat" group, minimal dehydration and maternal height for the "thin" group and tibial skinfold thickness in the "bigheaded" group but none of these results reached statistical significance.

(D) Conclusion

Detailed analysis was carried out for an arbitrary classification of growth based on the relative difference in centile position of three anthropometric measurements. A variety of trends was demonstrated but were not statistically significant due to the small numbers. The practice of looking for abnormal fetal growth by assessing the relative centile position of head circumference, birth weight and crown-heel length is quite often used in clinical practice; in this study it does not seem to be very helpful as a guide to impaired fetal growth.

(iv) The Incidence of Clinical and Morbidity Characteristics when Infants were Classified by a Divergence of at Least Two Centile Positions

In this section, infants were classified according to divergence of at least two centile positions, e.g. where length and weight were on the 50th centile, head circumference would be below the 10th. These infants were arbitrarily defined as showing a severe discrepancy: 35 LBW infants and 40 controls fell into this category and are shown in Table V 12. There was a highly significant difference in the distribution, there being an excess of "short" controls and "thin" LBW infants ($p < 0.005$).

A similar analysis was carried out as in the previous section and an attempt was made to delineate the clinical and morbidity patterns when analyses were carried out for preterm and term LBW infants and for controls.

(A) Preterm LBW Infants

As the number involved was only 13, detailed analysis was impossible, but amongst "smallheaded" infants there was an excess of minor abnormalities ($p < 0.025$), when compared with "appropriate".

(B) Term LBW Infants

In the group of 22 LBW babies, 15 were "thin" and though maternal disease, abortion and fetal distress were increased in this group, the results were not significant.

(C) Total LBW Group

Because the numbers of preterm and term LBW infants were so small the features of the total LBW group were studied. There were 35 LBW infants and, as might be anticipated, the predominant group were "thin" (19). Significant differences were found for minor abnormalities in "small-headed" and "thin" when compared with "appropriate" ($p < 0.05$) and for RDS ($p < 0.025$). It was noted that there was an excess of abortions amongst "short", "fat", and "thin" groups.

(D) Controls Infants

There was a tendency towards an excess of short infants and an increase of maternal disease, minor abnormalities and fetal distress, but these results did not reach statistical significance.

(v) Conclusion

When fetal growth is defined by this method, it tends to emphasise the baby who is defined as "thin" and who may only be showing a disproportionate weight loss in comparison to head size and growth. This may be due to a relative undergrowth for gestational age in all these measurements or to minor variations when growth has proceeded normally. This may occur in controls where an infant may be defined as "thin" because of a birth weight on the 75th centile and length and head circumference on the 90th centile. By any standards such an infant would be well grown.

Defining IUGR by this method might appear attractive but is clearly insensitive to the biological variation which occurs in the LBW population. It is concluded that this approach to the definition of IUGR is inappropriate and creates difficulties in an already confused field.

(3) Severe Intrauterine Growth Retardation

(i) Introduction

Intrauterine growth retardation (IUGR) has been variously defined as a birth weight falling below the 10th centile, below the 5th centile and more than 2 standard deviations below the mean (approximately the 3rd centile). Several authors have preferred the last definition, these infants being arbitrarily described as showing "severe growth retardation". It has been widely assumed that the more severe the IUGR, the greater the incidence of perinatal problems, and certainly on theoretical grounds infants in the lower centiles might be expected to have a higher morbidity rate.

(ii) Present Study

A detailed examination was made of the physical and morbidity characteristics of those infants with birth weights falling below -2 standard deviations from the mean weight for gestational age. An infant was defined as showing "severe IUGR" if the birth weight for gestation fell below -2 standard deviations when compared with the data of Gruenwald and Minh (1961). Thirty-three cases of "severe IUGR" were recorded: they were found exclusively among term infants. The lack of any controls was not surprising as the selection factor for control infants was a birth weight greater than 2.5 kg. The absence of any preterm infants amongst the severely growth retarded infants is hardly surprising because only 18 preterm infants were below the 10th centile and the chance of any of them falling below -2 standard deviations was thus relatively small.

(A) Maternal Characteristics

(a) Stature

The mothers tended to be shorter than those of the total LBW population. 15 out of 33 (45.5 per cent) were short, 14 out of 33 (42.4 per cent) were of medium height and only 3 (9.1 per cent) were tall (Table V 13). The birth weight adjustment for maternal height was 68.3 SD 128.8 g and for maternal height and midpregnancy weight was 95.5 g SD 134.1 g, which is similar to the term LBW group where severe IUGR has been excluded (Table V 14).

(b) Smoking

With regard to maternal smoking habits, there tended to be a deficiency of non-smokers and an excess of heavy smokers in this group (Table V 15), but the difference from the total population did not reach statistical significance.

(c) Other Pregnancies

Of the 33 mothers, 28 were known to have had a total of 55 live-born infants, of which 12 were LBW. This indicates a 21.8 per cent chance of such mothers delivering another LBW infant, a similar risk to that of the other term LBW mothers (23.2 per cent).

(B) Maternal and Neonatal Morbidity

There was no overall statistical difference between the morbidity pattern of infants with severe IUGR+ and that of the term LBW population. It was noted that there was a slightly increased incidence of abortions, maternal disease, hypertension and fetal distress and a lower incidence of minor abnormalities but none of these differences was statistically significant.

(C) Clinical Characteristics

A number of clinical characteristics were studied, viz, skin at micro-level, lateral scalp veins, tibial skinfold thickness, breast size and skin hydration. With the exception of the last, no significant difference was found when comparing these findings with those for term LBW infants.

(D) Comparison of Relative Centile Positions for Occipito-Frontal Circumference, Crown-Heel Length and Birth Weight

When the infants were defined according to centile position for occipito-frontal circumference, crown-heel length and birth weight, it was found that those with severe IUGR were similar in distribution to the term LBW population.

(iii) Discussion

Infants defined as showing severe IUGR according to the Gruenwald and Minh tables are likely to be more severely growth retarded than those defined on the basis of less stringent criteria.

The maternal characteristics in the severely growth retarded group were similar to those in the term LBW group who, with one exception, were all below the 10th centile. There was no difference between the two groups in maternal and neonatal morbidity patterns or in neonatal clinical characteristics. Thus it was not possible to identify a sub-group of infants with specific characteristics.

There are a number of possible reasons for this failure to demonstrate a relationship between perinatal problems and the degree of growth retardation. Infants showing severe IUGR were relatively few in number and though all cases with birth weight below 2500 g were included, a number over 2500 g may have been excluded. If one assumes that severe IUGR affects 2 per cent of the population, then approximately 50 cases per year would be delivered in the city of Aberdeen. The discrepancy between the anticipated 50 and the observed 33 cases may be partly accounted for by deaths and partly by infants with birth weights in excess of 2500 g. A further reason may be that the small size of the population conceals any morbidity trend. Lastly, it seems likely that severely growth retarded infants form a very heterogenous population which may vary from time to time. Rubella is a good example of an aetiological agent that has a cyclical pattern.

(4) Cluster Analysis

The clinical identification of individual sub-groups was a major objective of the low birth weight study. Due to the extent and complexity of the data, computer facilities were used in the cluster analysis. An H GROUP programme was chosen because it is designed to deal with the problems of profile similarity and utilises the total within group variation which is minimally increased at each step. The programme depends upon a generalised distance function between the groups and is based on the concept of the error of the squares (Veldman, 1967). Such an analysis does not appear to have been carried out previously.

Over 200 items identifying physical or disease characteristics were used in the cluster analysis to generate the different sub-groups. Once the stage had been reached where six individual sub-groups had been defined, each group was analysed statistically (results were only presented for statistical extremes) to identify the important characteristics. The analyses were made for control, total LBW, preterm LBW and term LBW infants, a new programme being run on each occasion. Thus no relationship exists between group G1 in the control, total LBW, preterm and term groups.

(i) Control Infants

The control population was subjected to a cluster analysis programme and a detailed statistical analysis was carried out at the six group stage. As might be anticipated there was very real similarity between the individual groups. Though many results were statistically significant few were of clinical importance (see Table V 16). A disparity of over 400 g existed in birthweight between G2 and G4; 1.5 weeks for gestation (G2 and G6); 1.3 cm for OFC in group G4 and G6; 1.6 cm for crown heel between G4 and G6. Impressive differences ($p < 0.001$) were noted for the TMS but once again the maximum difference was only 1.5 weeks (G4 and G6).
Analysis of other clinical items were not particularly helpful except for the growth retardation index. (The index was made up of a number of clinical signs considered to have a relationship with intrauterine growth retardation) As might have been expected G6 showed evidence of a higher IUGR index. On the basis of anthropometric and gestational measurement groups G4 and G6 appeared to differ in many respects from each other but other disease contributions did not occur with greater frequency.
Of some interest was the finding of an excess of mothers who smoked during pregnancy in group G8; there was also a higher incidence of clinical dehydration in this group (Table V 16).
It is therefore concluded that despite these differences control infants are drawn from a homogeneous population.

(ii) Total Low Birth Weight

The total low birth weight sample was subjected to the H GROUP programme and more detailed analysis was carried out at the 6 group stage (Table V 17). The effects of gestational age are very obvious, viz. a relatively small group clustering at 30 weeks, a larger group at 34 which showed highly significant differences between themselves and the three separate groups clustering at 36 weeks, 37 weeks and 38 weeks respectively. Three infants clustered in a separate group but this was due to a larger amount of unrecorded data in each case. This group was not included in the statistical analysis.

As might be expected, birth weight, occipito frontal circumference and crown-heel demonstrated significant differences between G5, G7 and the other groups. Crown-rump measurement of G5 showed statistical differences with the remainder, and with the total maturity score G5 showed marked differences whilst G2 and G7 were similar to each other but showed significant differences from the remainder. Numerous statistical significances were obtained for many other of the anthropometric analyses but these did not reach clinical significance.

Group 5

Group 5 consisted of 16 infants with a mean gestational age of 30.6 weeks. The anthropometric measurements and total maturity score were consistent with delivery at that period of gestation. The weight-for-gestation centile was approximately on the 25th centile. Clinically the infants were oedematous and were deficient in subcutaneous tissue - probably due to lack of deposition rather than loss of normal hydration and texture. The sagittal sutures tended to overlap. These infants showed a low intrauterine growth retardation index. There was a high incidence of respiratory distress and concomitant intravenous therapy. In conclusion, this group showed all the characteristics of short gestation.

Group 7

This group was made up of 26 infants delivered at a mean gestational age of [illegible] weeks and, like the previous group, their anthropometric and external characteristics were consistent with the length of their gestation. The infants had normal subcutaneous tissue and showed no evidence of intrauterine growth retardation. A number of these infants required intravenous therapy, in part due to a moderate incidence of respiratory distress. It seems that the characteristics of this group were appropriate to their gestational age.

Group 2

This group was made up of 37 infants with a gestational age of 36.3 weeks. The mean birthweight was very similar to that of the remaining two groups of longer gestation but the head circumference was significantly less. The group showed slight subcutaneous tissue loss and early evidence of skin changes and suture separation. The intrauterine growth retardation index was low (2). The mothers of this group smoked in moderation but had a significantly high incidence of pre-eclamptic toxaemia.

Group 1

This group comprised 43 infants, and showed significant evidence of intrauterine growth retardation. The anthropometric measurements were consistently reduced and there was clinical evidence of subcutaneous tissue loss, minimal dehydration, superficial skin changes and sagittal suture separation. This was corroborated by a high IUGR index. The mothers of this group smoked significantly more than the previous groups.

Group 4

The remaining major group consisted of 24 infants at a gestational age of 38.4 weeks. Once again there was considerable reduction in the anthropometric parameters. In many ways this group was similar to the preceding one and likewise showed a high intrauterine growth retardation index. As a group, themothers tended to smoke excessively and this may have been a factor in the aetiology of their low birth weight.

Group 93

This very small group consisted of three infants who clustered together because of unrecorded data. As might be anticipated, there was a high incidence of respiratory distress and illness which made examination difficult.

(iii)Preterm LBW

A similar cluster analysis was carried out for the preterm LBW infants (Table V 18). The influence of gestational age is inevitably greater in the preterm group. At the six group clustering, 4 major groupings were apparent -

a very immature cluster at about 30 weeks of gestational age which was significantly different from the other groups, ($p < 0.05$). Two groups (with a mean gestational age between 32 - 34 weeks) were not statistically different from each other but differed from another two clustering at about 35 weeks. Group 6 was significantly different from all the other groups in respect of birth weight, OFC, crown-heel and rump. Each of these parameters was a significant but not consistent difference between each of the other groups. When studying the total maturity score (TMS) three overall groups appeared, G6 with a score of 9, G1 and G2 scored 15 and G9 and G30 scored just over 21.

Group 6

This group was made up of 14 infants with a clinically confirmed gestational age of 30 weeks. The characteristics were those of immaturity and the infants demonstrated external and anthropometric characteristics appropriate for their gestational age. As might be anticipated, there was a high incidence of oedema and intravenous therapy. Rather surprisingly this group had the lowest mean skinfold thickness, which probably reflects the lack of fat since deposition does not occur in appreciable amounts until after the 32nd week.

The next 2 groups, 2 and 1, were very similar in their characteristics.

Group 2

Consisted of 26 infants with a gestational age of 33 weeks. The salient feature of this group is the predominance of male infants (25/26).

Group 1

Consisted of 16 infants with very similar characteristics to group 2 but all the infants were females.

Groups 9 and 30 were also similar to one another in their characteristics.

Group 9

Made up of 9 infants with thin skinfold thicknesses but a relatively low IUGR index compared with group 30. This group had the lowest mean glucose level.

Group 30

Consisted of 5 infants. Characteristically they were longer than infants in group 9, showed more tibial skinfold wasting and had a significantly higher IUGR index ($p > 0.05$). Of all the groups, G30 showed most clinical evidence of intrauterine growth retardation.

Group 41

Consisted of 3 infants who clustered because of lack of clinical information and further detailed analysis is not possible.

(iv) Term LBW

The clinical characteristics of the term LBW group were studied in depth and four major categories were identified and are shown in Table V 19.

The length of gestational age was similar in all groups with the exception of G23, which in statistical terms had a significantly longer mean age. In both statistical and clinical terms, birth weight, occipito frontal circumference and crown-heel length were similar. The total maturity score once again demonstrated a number of statistical differences, but these findings were unimportant in clinical terms with the exception of Group G25. It is possible that the maternal dates in this group were mistaken.

G25 appeared to have many of the characteristics of normal infants delivered at 37 weeks gestation; in the main they were generally better nourished than any of the other groups. G2 was at the opposite extreme and demonstrated most clinical evidence of growth retardation. Groups G3 and G23 showed similar but less pronounced characteristics of growth retardation. G1 was comparable with G2 in gestational age but was of normal nutritional status: however, this group demonstrated an excess of perinatal problems. G4 comprised a single baby who showed highly atypical characteristics. In the next section a detailed statistical analysis is presented.

Group 25

Made up of 17 infants who appeared to have been born significantly early, as judged from the total maturity score ($p < 0.01$). The general characteristics of this group suggest a shorter gestational age than indicated by calculation from the last menstrual period and show lack of the features typical of IUGR. Subcutaneous tissue was more abundant, superficial skin changes less pronounced, ponderal index higher and the IUGR index was significantly lower than in the other groups.

Group 2

Made up of 23 babies who showed the most extreme signs of IUGR. There was a significant excess of clinical signs usually associated with growth retardation, such as superficial cracking of the skin, minimal dehydration, subcutaneous and tibial tissue loss. The IUGR index (4.4) was significantly raised in this group. A low ponderal index was a feature, as was the excess of mothers of this group who smoked ($p < 0.05$). As might be anticipated, the group had the lowest mean glucose 47.4 mg ($p < 0.001$).

Group 3 and Group 23

Comprised 11 and 10 infants respectively. Both these groups of infants showed evidence of growth retardation but not to the degree seen in group 2.

Group 1

Included 14 babies displaying many characteristics of normal fetal nutrition. The incidence of oedema was significantly higher than in any of the other groups. Neonatal illness was more frequent but did not reach statistical significance.

Group 4

Consisted of a single infant demonstrating evidence of extreme IUGR. This infant weighed 740 g at birth and gestatinnal age was 38 weeks. The unusually high ponderal index (2.8), reflected a very short crown heel length. This infant showed extreme hypoglycaemia.

(v) Discussion

The use of cluster analysis techniques seems appropriate when trying to identify groups of infants with specific characteristics. The major theoretical difficulty arises from problems of weighting. Certain characteristics may have a very much greater range - for example, birth weight or gestational age - compared with 5 variables for certain items of the total maturity score and only 2 for the presence or absence of disease conditions. In this analysis the programme was not weighted and a number of interesting sub-groups were obtained, particularly a group of infants of very short gestation and a group amongst term LBW infants showing clinical evidence of severe growth retardation. The potential value of cluster analysis relates mainly to long term follow-up. Developmental data obtained at 9 months were analysed according to each sub-group but failed to show any significant correlations. This was not unanticipated, since factors such as neonatal hypoglycaemia, which do not significantly affect a child's growth performance at 9 months, may nevertheless significantly reduce the child's IQ at 7 years of age. As far as we are aware, this is the first time that a cluster analysis programme has been utilised in the definition of intrauterine growth retardation. Its major advantage is the capacity to deal with a great deal of information by computer but the difficulty of differential weighting has not been fully overcome. An ongoing analysis is being currently undertaken.

(5) The use of Maternal and Neonatal Morbidity Patterns and Clinical Items in the Identification of Sub-Groups of LBW Infants

A wide variety of clinical features were studied in an attempt to identify groups of infants with specific problems. Almost every individual item recorded in the study was analysed: a number produced weak associations with the clinical and physical appearance of the baby but none of these items reached statistical significance. Of the more interesting results, neonatal Apgar score, apnoea, bilirubin, fetal distress, hypoglycaemia, respiratory distress syndrome, intrauterine growth retardation index, items of the total maturity score and general anthropometric measurements were studied. A number of maternal disease conditions were subjected to a similar analysis. Of these, abortions, antepartum haemorrhage, urinary infection, pre-eclamptic toxaemia and other maternal disease conditions did not show significant associations. Detailed analysis of a number of general maternal features, such as height, smoking patterns and pregnancy number, similarly failed to reveal groups of infants with specific characteristics.

It is concluded that the use of individual physical or disease characteristics of either mother or baby does not help to identify individual sub-groups. However, it is possible that such sub-groups exist but are not apparent in a sample of this relatively small size.

Conclusions

One of the main purposes of this study was to try to define intrauterine growth retardation more precisely. In this chapter eight different methods were investigated, ranging from the simple and widely used criterion of weight for gestational age to anthropometric ratios, computer clustering techniques and the use of individual maternal and neonatal clinical and morbidity patterns. It is accepted that an improved definition must recognize and take into account differences in etiology, clinical appearance and likely complications.

Part of the difficulty in arriving at a new definition is made clear by consideration of work carried out in animals, especially experimental studies of the fetus following occlusion of the arterial supply or as a result of maternal nutritional deprivation. By contrast, work with the human fetus is complicated by the multiplicity of uncontrolled variables, such as relative undernutrition, maternal smoking and late onset pre-eclampsia, all of which may have effects on the fetus at different times and to different extents. A detailed list of the great number of conditions known to be associated with impaired fetal growth does not seem relevant to this thesis. Indeed, the very breadth of definition of intrauterine growth retardation has encouraged the inclusion of diseases which probably have little if any effect in retarding intrauterine growth.

Inability to define intrauterine growth retardation with any degree of precision makes it difficult to assess many procedures carried out in pregnancy. Some obstetricians claim a very high success rate in the recognition of intrauterine growth retardation by methods currently available. However it must be pointed out that prediction by using simple indices such as maternal height, smoking and a previous low birth weight baby, can itself result in a high success rate. Inability to define with precision the different groups of growth retarded newborn babies should not prevent us from focussing attention on mothers who take steps to improve their general wellbeing during pregnancy or from attempting timely intervention if impaired fetal growth is thought to be occurring. The imprecision of present definitions constitutes a handicap to research workers using them to assess results. Nevertheless there are some advantages of the current definitions and these should be fully exploited.

CHAPTER VI

SIBLINGS OF LBW INFANTS

(1) Outcome of Other Pregnancies in Mothers of LBW Infants

Maternal factors strongly correlated with LBW include social class, height, smoking habits, pregnancy number, antepartum haemorrhage, pre-eclamptic toxaemia. Fetal factors include twinning, infection and congenital abnormalities. These have all been studied in some depth and there has been recent work on the pregnancy outcome of individual mothers. Ounsted (1965) propounded a theory of maternal constraint based on the classical animal experiments by Walton and Hammond (1938). Turner (1971) drew attention to the adverse effect of intrauterine rubella on fetal growth rates when compared with those of siblings. It was considered that further insight into the mechanisms of fetal growth might be obtained by studying pregnancy outcome for siblings of infants in the LBW cohort.

A search was made of the Aberdeen Maternity Hospital records for the birth histories of siblings of index and control infants. Due to the demographic characteristics of Aberdeen mothers, the majority of siblings were born in the same hospital and accurate birth histories were available through the system of record linkage. Of the 149 mothers of LBW infants, it was possible to trace 116 (77.8 per cent) with 242 pregnancies, 201 of which ended with live births. Of the matched control, 118 mothers (79.2%) having 20.3 pregnancies were traced; 176 of the pregnancies ended with a liveborn child. A surprisingly high rate of LBW occurred in the siblings of LBW infants, 49 out of 201 compared with 18 of 176 controls, which included three sets of twins. The 49 repeated LBW deliveries occurred in 41 mothers and the 18 in the control group involved 12 control mothers.

The siblings were classified as preterm (PT), preterm intrauterine growth retardation (<10 centile) (PTIUGR) and term intrauterine growth retardation (<10 centile) (TIUGR) but not necessarily of LBW or normally grown (NG). Intrauterine growth retardation was said to exist if the weight by gestational age was below the 10th centile on the Thomson, Billewicz and Hytten tables (1968).

(2) Fetal Growth Patterns of Siblings

The fetal growth patterns of siblings were analysed in relation to the LBW sample and the following patterns of reproductive outcome emerged.

(i) Pregnancy outcome of control mothers with normally grown fetuses

It was assumed that control infants were normally grown, see Table VI 1, but certain maternal characteristics showed deviations when compared with a so-called normal population. The control mothers smoked more and were of lower social class and shorter stature than the general population but despite this they had a lower incidence of PT and IUGR delivery.

(ii) Pregnancy outcome of mothers of LBW infants with a preterm delivery

From Table VI 2 it appears that preterm delivery is non-repetitive but these mothers have the highest rate of abortion (22.2%). The slight excess of IUGR (14.4%) is due to the clustering of factors in a cohort of LBW infants which are known to depress the rate of fetal growth.

(iii)Pregnancy outcome of mothers of LBW infants with a preterm delivery and IUGR

Though the number of pregnancies in the group of PTIUGR is small (40), such mothers have low rates for both IUGR and abortion, Table VI 3. The data suggest that PTIUGR is a sporadic occurrence and that the cause of the IUGR is not the maternal organism, as in the term LBW, but a chance association with, for example, a chromosomal abnormality.

(iv) Pregnancy outcome of mothers of LBW infants with a term IUGR delivery

Mothers giving birth to term IUGR fetuses have a 23.2 per cent chance of a similar event occurring in another pregnancy: this may reach 27.6 per cent when preterm IUGR live births are considered as well, Table IV 4. The results support Ounsted's theory of maternal constraint. Despite careful matching for factors involved in fetal growth, the controls smoked less, were taller and were of higher social class than the LBW mothers and, in contradistinction to Ounsted's opinion, it is felt that these factors contribute slightly to impaired fetal growth.

(v) Summary

Preterm delivery, though non-repetitive, is associated with an increased tendency to abortion. In contradistinction, IUGR is strongly associated with a similar outcome in other pregnancies. The control population have lower rates of preterm birth and IUGR than the general populatinn. It might now be possible, by analysis of the low birth weight data, to identify infants belonging to growth retarded sibships and determine their neonatal characteristics.

(3) The Characteristics of LBW Infants where another Sibling has been LBW

(i) The characteristics of mothers giving birth to growth retarded and LBW infants have been well documented. It is well known that preterm delivery giving rise to LBW may be associated with cervical incompetence but such situations are relatively rare, and amongst the "idiopathic group" there is an increase in subsequent short gestation which does not reach statistical significance. The propensity for mothers of growth-retarded infants to restrict the growth of subsequent fetuses is well known and though low social class, short stature, smoking and female sex of the infant may all contribute to the low weight, there appear to be other factors at present unknown. The outcome of other pregnancies has been discussed earlier in the chapter and here it is proposed to consider the characteristics of both mother and infant where another sibling is of low birth weight.

(ii) Procedure

Initially, all pregnancies with repeated LBW infants were studied irrespective of the duration of gestation. Forty-one mothers were identified as having given birth to at least one LBW infant, their overall total being 49 LBW infants. These were divided into preterm (8), repeat preterm (8 cases); preterm, repeat term (5); term, repeat term (9); term, repeat term (7). The remaining 12 cases could not be classified because either a mixture of term and preterm siblings or the duration of gestation was unknown. The different categories are outlined in Table VI 5.

There was a small group of control mothers (12) who gave birth to LBW infants in other pregnancies and, despite their relative scarcity, these were used as comparisons.

(iii) Maternal Characteristics

The mean maternal height adjustment for the total LBW repeaters was 94.5 g SD 140.1 g, which was similar to that for the controls (92.7 g SD 106.8 g) (see Table VI 6). The height adjustment amongst preterm repeaters was 58.1 g SD 139.7 g, compared with the height adjustment for term LBW infants of 123.0 g SD 133.6 g, the difference not being significant. When height and midpregnancy weight for term LBW infants (170.5 g SD 155.8 g) was compared with the adjustment for controls (48.0 g SD 150.2 g), there was a significant difference ($p < 0.05$), Table VI 7. Birth weight could theoretically be increased for maternal height and mid-pregnancy weight in 66 per cent of cases was similar for preterm, term and total LBW. Maternal smoking patterns were also similar amongst mothers of LBW repeaters when compared with the total LBW population. When considering social class, there was a marked deficit of social classes I, II and IIIa (4 out of 41), which was balanced by an excess of social classes IV and V (22 out of 41) but this was no different to the rest of the LBW population.

(iv) Maternal and Neonatal Morbidity Patterns

It is difficult to categorise the disease patterns of the individual groups, due to the small number available for study. The morbidity characteristics of the mothers giving birth to repeated preterm infants were, as might be anticipated, typical of such a group. The other groups were too small to carry out statistical analysis.

(v) Clinical characteristics

There did not appear to be any significant differences in the clinical features of the infants between any of the sub-groups.

(vi) Discrepancy in centile position

When the LBW repeaters were examined for discrepancy of centile position in relation to birth weight, head circumference and crown-heel length, there appeared to be a relative excess of babies in whom all three measurements were at the same centile positions, i.e. who were appropriate for gestation (12 out of 41). There were also excesses of infants classified as "big head" (10 out of 41) and of those whose head circumference was relatively greater than length and weight, matched by deficits in other groups, particularly those described as thin (4 out of 41). This finding probably reflects the combination of term and preterm LBW infants with their differing distribution of characteristics.

(vii) Discussion

The outcome in other pregnancies was studied to assess whether those mothers with repeated LBW births differed in any way from the rest of the LBW group. 41 such mothers were identified, with a total of 49 LBW deliveries; nearly half of the mothers had either "preterm, repeat preterm" or "term, repeat term" deliveries; the remainder were divided between at least five other variations, making statistical analysis impossible.

Factors influencing fetal growth, such as maternal height, maternal height and midpregnancy weight, smoking and social class, were studied and did not differ significantly from those in the general LBW population. However, it has already been shown that the total low birth weight population differs significantly from the controls. When maternal and neonatal morbidity patterns were studied for each group, those with the "preterm, repeat preterm" pattern were typical of mothers who had early deliveries. Mothers delivering first a term baby and then a preterm one appeared to have a high incidence of maternal disease before and during pregnancy, but the numbers were too small for statistical analysis.

Ounsted (1965) studied 90 women giving birth to infants weighing less than 2 SD below the mean and noted minor differences in factors known to influence fetal growth when compared with her control population of 225 unselected women, namely fewer upper social class and more mothers who smoked amongst her growth retarded group. She felt this was insufficient to account for the repeated patterns of restricted fetal growth and postulated maternal constraint as the mechanism responsible. Further analysis of her data shows that in many respects the background of her growth retarded series was worse (though not reaching statistical significance) than that of her controls. One is left with the strong impression that the mothers of her growth retarded babies were not achieving their full biological potential due to a variety of background factors. It seems reasonable to postulate that mothers of low birth weight infants are a different population from their control peers and the evidence presented in Chapter IV would support such a statement. Recently Johnstone and Inglis (1974), in a study of 185 index cases of LBW in which siblings were identified, noted that sisters of mothers giving birth to growth retarded infants also had children with relatively reduced fetal growth rates, but this did not hold for the wives of their brothers. These authors concluded that a familial component operates on the female side in growth retardation, but, on the other hand, might possibly be dietary or some other microsocial factor.

Conclusions

A study of siblings of low birth weight infants shows that preterm delivery is non-repetitive, although it is associated with an increased tendency to abortion. It contradistinction, IUGR is strongly associated with a similar outcome in other pregnancies. Study of the characteristics of low birth weight infants where another sibling has been of low birth weight failed to demonstrate any specific features.

CHAPTER VII

THE SIGNIFICANCE OF GESTATIONAL AGE

(1) Gestational Age as a Guide to Maturity

Gestational age at birth (GA) is widely considered to be the simplest indicator of maturity in the newborn infant. However, serious difficulties may arise from the erroneous belief that gestation is synonymous with maturation as was recognized by the World Health Organisation (1961) when they abandoned the term "prematurity", substituting "low birth weight", which at least is directly measurable. There are two major problems in determining gestational age, firstly, the inability of many women to remember the date of their last menstrual period (LMP) and, second, the fact that not all pregnant women have ready access to and the ability to use a calendar. The accuracy of the LMP depends upon maternal memory and has been variously estimated as ± 4 days in 92 per cent of women (Butler and Bonham, 1963); ± 5 days in 84 per cent (Neligan, 1965); and with reasonable accuracy in 80 per cent (Holt, 1965) though in only 30 per cent in certain developing countries (Singer, Blake and Wolfsdorf, 1973).

It is well known that use of the LMP is liable to errors which may cause inaccuracy. For example, women tend to select certain days of the months with greater frequency than might be expected from chance. Frazier (1959) showed that women were biased towards selecting the 1st and 15th days of a lunar month and to a lesser extent the 10th, 20th and 25th days. They recorded one of these five days in 30 per cent of cases when the random expectation would have been 18 per cent.

Estimation of the duration of pregnancy is based on the assumption that women ovulate on the 14th day of the menstrual cycle, but Corner, Farris and Corner (1950) found that ovulation, as indicated by urine testing and histological examination of the ovaries and endometrium in a small sample of women (39), ranged from the 8th to the 20th day of the cycle; the majority were between 11 and 14 days with the maximum on the 13th day.

The LMP tells us no more than age does in any other biological situation, namely that certain physiological events may be anticipated because a certain stage of chronological development has been reached. In the past, estimates of so-called "fetal maturity" have been largely based on anthropometric measurements or on estimates of excreted products which reflect the biological performance of the organism. Description of the lecithin sphingomyelin ratio (LS) by Gluck et al (1971) provided for the first time a direct indicator of fetal maturation. More recently fetal stress tests have been evolved and their effects assessed by recording the patterns of the fetal heart rate. These tests are likely to prove of more than theoretical interest, but like the L/S ratio will only be applied to a small number of selected patients. Thus, as in all studies of fetal growth, one comes back to the simple universally available criterion with all its limitations - gestational age based on the LMP.

When using GA as a yardstick in studies of low birth weight, the criterion of selection of the sample may have significant bearing on the results. Since the present LBW sample was selected by weight (2500 g or less), infants of above average fetal growth delivered after 34 weeks (50th centile = 2.47 kg.) would be excluded (Thomson, Billewicz and Hytten, 1968).

(2) Distribution of the Sample by Gestational Age

The case records of all the LBW and control infants were examined by an obstetrician (Dr. K.J. Dennis) and the date of the

LMP as stated by the mother was either accepted as certain or classified as uncertain due to some discrepancy in the history of clinical examination. Tables VII 1 and VII 2 show the distribution of the control and LBW infants by week of gestation and by certainty or uncertainty of the LMP.

Of the control population 98 of 149 (65.8 per cent) were certain compared to 51 (34.2 per cent) uncertain (Table VII 1) in comparison to the LBW group where 91 of 149 (61.1 per cent) were classified as certain as compared to 58 (38.9 per cent) uncertain (Table VII 2). The degree of uncertainty in the present sample is higher than in previous studies and probably reflects the more stringent criteria applied to the definition of the LMP. Thus in previous studies some degree of latitude was allowed, e.g. ± 4 days in the British Perinatal Mortality Survey (Butler and Bonham, 1963) and ± 5 days by Neligan (1965), whereas in the present study "certainty" was defined as ± 0 days.

The mean and standard deviation of GA are shown in Table VII 3; the anticipated difference is found between control and LBW populations. No significant difference in the mean GA was found between "certain" and "uncertain" categories.

The mean GA in completed weeks for controls is 39.7 weeks (SD 1.1), for preterm babies 33.2 weeks (SD 2.5) and for term LBW babies, 38.4 weeks (SD 1.1). No significant differences were found in mean GA between "certain" and "uncertain" groups for control infants total LBW or term LBW. There was a significant difference ($p < 0.05$) between preterm LBW, certain and uncertain (Table VII 3).

In earlier studies, mean values for GA were seldom calculated and are not always easily ascertained. However, with the recognition of the problem of impaired fetal growth, GA data are being given more precisely, e.g. Fitzhardinge and Steven (1972), and Dweck et al (1973).

The comparison of the means and standard deviations for term LBW and controls is of considerable importance, because detailed comparison will later be made between morbidity patterns and physical characteristics in an attempt to identify more precisely the special features of the growth retarded infant.

(3) Morbidity Patterns and Gestational Age

Gestational age is always likely to be the yardstick against which morbidity patterns are assessed and is particularly important in any study of LBW infants. The morbidity patterns for infants delivered at 28 weeks are very different from those for infants delivered at 33 weeks of gestation, so that the inclusion of even a slight excess of the former may significantly influence the interpretation of results. Throughout the analysis constant reference is made to the GA graphs to determine whether GA was the operative factor.

Single items, such as the incidence of maternal disease, can be shown in graphic form but physical characteristics tend to have a wide range of values for each individual item, e.g. skin wasting, and are not easily displayed graphically. They will therefore be presented in tabular form to highlight certain differences in clinical presentation between preterm LBW, term LBW and control infants. Mean and standard deviation values will be presented where appropriate.

(i) Morbidity patterns for LBW infants and controls by gestational age

Graphs for assisting analysis were constructed for both maternal and neonatal morbidity for LBW infants and controls from 27 weeks to term or, in some cases, in broad bands, viz: less than 30 weeks, 30-34, 35-37 and 38-42 weeks. Data on maternal disease, abortions, pre-eclamptic toxaemia, other hypertension, placenta praevia, antepartum haemorrhage, other antepartum haemorrhage and fetal distress were abstracted from the maternal histories, and data on cyanotic attacks, neonatal disease and Silverman score (a score of one or more) were derived from the neonatal histories. As might be expected, the shorter the gestation the higher the rate of neonatal and maternal problems. A detailed analysis between controls and term LBW of disease for each week was carried out (Table VII 4 and 5) and showed the excessive morbidity of term LBW when gestation has been taken into account. Of the 10 morbidity items, eight show a highly significant difference between term LBW infants and controls (Table VII 6).

(ii) The influence of certain and uncertain gestational categories on maternal and neonatal morbidity

The data were analysed to determine whether the maternal and neonatal morbidity differed significantly for the certain and uncertain gestational categories. In the event of the two groups having a similar morbidity, it was planned to combine them to give a larger group for further analysis. Using chi square analysis, no significant difference was found between certain and uncertain gestation groups either among controls or among preterm LBW infants. Among total LBW infants, a significant difference was found for maternal disease ($p < 0.01$). In term LBW infants, significant differences were found only for maternal disease ($p < 0.025$) and minor abnormalities ($p < 0.025$). It was therefore considered reasonable to combine the certain and uncertain groups for the purposes of further analysis.

Conclusions

It was considered reasonable to combine in a single group infants with certain and uncertain gestational age for purposes of further analysis, because their gestatinnal age, maternal and neonatal morbidity patterns were very similar.

CHAPTER VIII

THE CONFIRMATION OF GESTATIONAL AGE BY EXTERNAL PHYSICAL CHARACTERISTICS (TOTAL MATURITY SCORE)

(1) Introduction

Considerable research has recently been devoted to evolving methods of corroborating gestational age as calculated from the date of the last menstrual period (LMP). These range from the use of ultrasound, X-rays and amniotic fluid estimations during pregnancy, to biochemical and clinical procedures in the newborn infant. The latter can be divided into three main groups - biochemical, anthropometric and non-anthropometric.

Some biochemical investigations correlate reasonably well with gestational age, e.g. measures of α_1-fetoprotein (Norgaard-Pedersen, 1973) and fetal haemoglobin (Brody, 1960). Many authors have described anthropometric measurements (e.g. Parmelee et al., 1964): head circumference has the highest correlation with gestational age, followed by crown-heel length and then birth weight: skinfold thickness correlates very poorly (Gampel, 1965), due to the effects of intra-uterine growth retardation (IUGR). The non-anthropometric methods have been arbitrarily divided into two groups. The first comprises those methods which require sophisticated equipment - X-ray examination of the epiphyses (Christie, 1949), electro-encephalographic studies (Dreyfus-Brisac, Flescher and Plassart, 1962), auditory evoked responses (Graziani, Weitzman and Velasco, 1968), photic stimulation (Engel and Butler, 1963), and motor nerve conduction (Dubowitz, et al., 1968). In the second group are a number of simpler clinical methods utilising external physical characteristics (Farr, Kerridge and Mitchell, 1966; Usher, McLean and Scott, 1966), neurological signs (Robinson, 1966) or both (Dubowitz, Dubowitz and Goldberg, 1970).

The purpose of this part of the study was two-fold: first, to corroborate the date of the LMP by using the total maturity score (TMS) of Farr, Kerridge and Mitchell (1966), which is based on external physical characteristics. Second, to assess the accuracy of the TMS as a method of estimating gestational age by comparing it with gestational age calculated from the date of the last menstrual period.

(2) Methodology

The TMS was calculated for all but one of the infants in the study. The method recommends that babies should be examined between 12 and 36 hours of age and the ages of the examination in this study are shown in Table VIII 1. One LBW infant and four control infants were studied before 12 hours of age and six LBW infants and two controls after the age of 36 hours: these deviations were due to illness in the LBW group and inconvenience in the control group (the control infants were examined in a maternity home at a distance from the main hospital and practical difficulties sometimes led to delays).

There was no significant difference between the mean ages at examination of the total LBW group and the controls ($p < 0.25$) but the mean age at examination of preterm infants was significantly higher than that of the term LBW infants ($p < 0.05$) due to illness in the former group (see Table VIII 1).

It was fundamental to the study that the examiner did not know the length of gestation as stated by the mother.

The data are presented and analysed in broad categories of preterm LBW, term LBW, total LBW and control infants. The statistical analysis of this section basically follows that in most other studies in the literature but differs in one important respect, namely, the separate analysis of the categories of preterm LBW and term LBW. In addition, statistical analysis was made of the difference between gestational age derived from the LMP and that calculated from the TMS in individual babies. This is a departure from most other studies, in which comparison has been made of the means and standard deviations of gestational age.

(3) Inter-Observer Reliability

Due to the long duration of the LBW study, it was necessary to involve two examiners: the majority of infants were examined by JIC (122 LBW and 121 control) and the rest by EJD (26 LBW and 28 control). The proportions of "certain" and "uncertain" dates of LMP in the pre-term, term and control groups were similar, though not identical, for the two examiners (see Table III 11).

Statistical comparison between the two examiners is not really valid because of the smaller numbers examined by EJD. The mean difference in gestational age calculated by the two methods for the control group was 0.19 SD 1.13 weeks for JIC and 0.65 SD 1.60 weeks for EJD: the difference between the two is not statistically significant ($p < 0.25$). Comparable data for the LBW group were 0.68 SD 2.10 weeks for JIC and 1.78 SD 1.87 weeks for EJD. This difference was significant ($p < 0.01$) and was thought to be due to EJD having examined rather more LBW infants with uncertain dates.

(4) Results

It was hoped that the clinical assessment of gestational age by TMS could be used interchangeably with age derived from the LMP in a number of subsequent analyses. Accordingly, the reliability of such a procedure was studied in two different ways.

(i) Comparison between mean gestational ages

(A) A comparison was made between the mean gestational ages calculated by the two methods in mothers who were certain of the date of their last menstrual period (Table VIII 2). The only significant difference was found in the pre-term LBW group - a mean gestational age by maternal dates of 33.15 SD 2.63 weeks compared with 34.74 SD 3.01 weeks by TMS ($p < 0.02$). The mean values for the other groups showed no significant differences. The wide Standard Deviation in the total LBW group compared with the control group reflects the influence of pre-term infants on the total group.

(B) A similar comparison was made for mothers who were uncertain about their last LMP and the results are shown in Table VIII 3. There is a difference of nearly two weeks between the means for the pre-term LBW infants which was significant ($p < 0.01$). This made the difference in the total LBW group significant, although the difference in the term LBW group alone was not significant, like that of the control group.

(C) When the same calculations were made for all cases in the study, the differences between the means for the total LBW group and for the control group were significant and the difference for the pre-term LBW group highly significant (Table VIII 4).

(ii) Comparison of the differences in weeks of gestational age

An analysis was made between the differences in weeks of gestational age when derived by the two methods (Table VIII 5). There was no significant difference between the two for any of the four groups, whether differentiated by whether the mother was certain or uncertain of her dates or whether considered as a total group of mothers.

(5) Conclusion

For term LBW infants and for the controls, gestational age calculated on the TMS appears to be a satisfactory substitute for gestational age calculated from the date of the last menstrual period. Certainly the difference between the two methods in the whole control group just reached the level of statistical significance ($p < 0.02$), but this represents a difference of only 0.3 weeks, which is not clinically important. The validity of such substitution in the pre-term LBW group is not so evident. One reason for this is that maturity scoring in pre-term infants is not so precise; for example, the total score at 31 weeks of gestation is only 8 compared with 28 at 40 weeks, so that a difference of one point in the score makes a far greater impact at the earlier age. The discrepancy in the pre-term group is not so great when the mother is certain of her dates and the difference then is only just significant ($p < 0.02$).

It is concluded that the use of the TMS is justifiable as a means of calculating gestational age, but it becomes progressively less reliable as the duration of gestation shortens.

(6) Discussion

The choice of the external physical characteristics in preference to neurological signs as a means of assessing gestational age was made for two reasons. Firstly, external physical characteristics are influenced by neonatal illness and the associated problems of treatment. Ill babies or those attached to intensive equipment cannot be held in ventral suspension or tested for head lag.

Neurological signs may be affected by drugs administered to the mother. For example, in 28 mothers receiving epidural anaesthesia (Lidocaine or Mepivacaine), significant differences were found in muscle tone (pull to sitting, arm recoil response to pin prick, quality of rooting and moro reflex) when compared with 13 infants in the non-epidural group (Scanlon et al., 1974). Of the external physical characteristics clearly skin colour and opacity can be influenced by illness and the assessment of lanugo hair may present difficulty. Second, the methods using external physical characteristics had been developed further than those based on neurological examination when the study was started, which was before the publication of the combined Dubowitz method.

The problem of determining gestational age as accurately as possible is fundamental to any study concerned with low birth weight. In a number of studies, the same investigator has examined the infant and questioned the mother concerning the details of her last menstrual period. Such a dual role inevitably influences the findings and it is felt that, despite the problems of organisation, the mother should be questioned and her records examined by an independent worker. In the present study a rigorous attempt was made to avoid gaining any knowledge of the maternal dates during the neonatal assessment. This can sometimes prove to be difficult in a special care unit where staff often refer to infants by either weight or gestational age rather than by name.

The external physical characteristics have been shown to correlate well with gestational age (0.76 ± 2.4 weeks in 95 per cent of cases) (Farr, Kerridge and Mitchell, 1966). Further evidence comes from the work of Usher, McLean and Scott (1966) who described five characteristics, four of which (plantar skin creases, breast nodules, cartilagenous development of the ear lobe, descent of the testes with ruggae of the scrotum) were included among the external physical characteristics used in this study. These authors found the five characteristics particularly useful in separating the border line premature from the full-term infant. In their study 226 malnourished infants, 97.4% were correctly identified as being delivered after 37 weeks (Usher, McLean and Scott, 1966).

In the present study, the external characteristics (TMS) had a good correlation with gestational age, namely a correlation coefficient of 0.76 was found for the total LBW group and of 0.72 for the pre-term LBW group. This compared favourably with the findings of previous studies and is a clear improvement on other non-anthropometric measurements of gestational age. However, the use of correlation coefficients has not been entirely satisfactory, as many studies have only included a very few babies at the shorter gestation. Confidence limits seem more appropriate but have usually been calculated on total samples rather than on subgroups defined as preterm and term as in the present study. It has not always been appreciated by previous investigators that the precision of the maturity score varies with gestational age since one point on the score represents one week up to 32 weeks of gestation and three points represents a week at term. In the present study, infants whose mothers were certain of their dates were divided into preterm and term groups and the means and standard deviations for gestational age calculated by the two methods were determined for each group. The standard deviation for preterm infants compared very unfavourably with that for the control group (2.63 weeks compared to 0.99 weeks). Thus the calculation of confidence limits may be very significantly influenced by the relative proportion of preterm to term babies. The present sample is perhaps unusual - due to selection factors - as it includes a large number of preterm infants (44/189) of certain gestation, whereas most other studies have been of consecutive births, and from theoretical considerations one would only expect about 10 per cent of such series to have been delivered earlier than 38 weeks (Butler and Bonham, 1963).

Consideration must be given to the combined scoring system devised by Dubowitz, Dubowitz and Goldberg (1970), who found that the combined score gave a slightly higher correlation (0.93 ± 14 days at the 95 per cent confidence limit) than either the external characteristics (0.91) or the neurological score (0.89). The difficulties of carrying out the neurological score in ill babies and the effects of maternal drugs on tone, nullifies any advantage. The validity of the combined neurological and extreme characteristics score has been confirmed by a number of workers including Hancock (1973) who studied 434 neonates (25 preterm) of certain gestation: the difference between assessment and the score was one week or less in 400, 1.5 in 26, and greater than 1.5 in 8. These reported findings are impressive but there must be a slight reservation because the examiner had in some cases prior knowledge of the gestational age (Hancock, 1973). The use of the Dubowitz score in twins by Keet, Jaroszewicz and Liebenberg (1974) showed the scores for each pair of twins to be similar. However, the prior knowledge that the subjects were twins may well have influenced the examiner to err towards making the scores similar.

The major weakness with all these attempts to assess gestatinnal age by clinical means has been the lack of sufficient numbers of preterm babies. However, despite such difficulties it is clear that gestational age can be determined in this way and it seems reasonable to use the method in place of calculations based on the mother's last menstrual period, when it appears appropriate to do so.

Conclusions

The use of external physical characteristics in the confirmation of gestational age is analysed and discussed. The total maturity score is a reasonable substitute for calculation based on the date of the mother's last menstrual period when the latter is not available.

CHAPTER IX

PHYSICAL CHARACTERISTICS, GESTATIONAL AGE AND GROWTH

Introduction

This chapter and analysis has been carried out on a number of non-anthropometric characteristics to assess their relationship to gestational age and the influence of fetal growth.

(1) Items of the Total Maturity Score Related to Gestational Age

The external physical characteristics of the infant which form the basis of the total maturity score (TMS) were considered in Chapter VIII. Here the relationship of these characteristics to gestation is examined by control, total LBW, preterm LBW and term LBW groups. The statistical significance of each relationship is shown in Table IX 1: all items show highly significant differences between the groups suggesting that both gestational age and fetal growth are major determinant factors. It has already been shown that control infants have a longer mean gestation than term LBW which would at least in part explain these differences. To exclude the influence of IUGR on the total maturity score a further analysis of each individual item of the score was studied in relation to the centile position of the baby. No association was found in the 72 term LBW infants falling either below the 5th or 10th centile, thus excluding the effects of IUGR on the score.

It was thought that IUGR might significantly influence the results of the TMS. To exclude this possibility, the mean gestational age of term LBW infants with scores of certain items of the TMS normally associated with shorter gestation was compared with the mean for all term LBW infants (38.4 weeks SD 1.1, see Table VII 2). Low scores (< 2) for skin colour, skin opacity, plantar skin creases, oedema and lanugo hair and high values (≥ 2)

for skin texture and breast size were studied (see Table IX 2). Skin texture was the only item to show a significant difference ($p < 0.05$) but this was to be anticipated as a high score is generally associated with prolonged gestation. It is concluded that the difference in the items of the TMS between term LBW and controls was due to gestation rather than IUGR.

(2) Other Physical Characteristics Related to Gestational Age

A study was made of a number of additional non-anthropometric physical characteristics to assess their relationship to gestational age. These characteristics range from the state of the sagittal suture to the length of the great toe. The influence of gestational age was assessed by comparing the preterm LBW group (mean gestatinnal age 33.2 weeks SD 1.1), the term LBW group (mean gestational age 38.4 weeks SD 1.1) and the control group (mean gestational age 39.7 weeks SD 1.1).

(i) Methodology

Separation of the sagittal suture was assessed by palpation with the forefinger and graded by degrees of separation, approximation and overlap.

The length of the scalp hair is measured in the region above the ear.

The appearance of the veins in the cubital fossa were quantitated by degrees of visibility, viz absent, just visible and obvious.

The appearance of the eyelids were described as oedematous, baggy, buried or normal.

The dermal pattern was defined as the degree of wrinkling of the skin determined by extending the thumb and forefinger over the skin of the upper abdomen and scoring in five grades. The linear appearance was assessed in degrees, ranging from complete absence -- to marked wrinkling +++.

The condition of the skin on the dorsum of the hands was made by direct observation for dryness, various degrees of cracking, superficial peeling and scaling.

The length of the first toe was compared with that of the second by gently squeezing the two toes between the thumb and index finger and observing which was longer.

Oedema was estimated by assessing the presence of pitting after at least 5 seconds of pressure.

(ii) Sagittal Suture

The extent of separation or overlap of the sagittal suture was assessed. A significant excess of overlap was found in preterm LBW infants when compared with controls ($p < 0.001$). The control group contained some infants with overlapping sutures (29/149) but there was a significant excess of approximated (39/149) and separated sutures (81/149), see Table IX 3. Thus overlapping of the cranial sutures was noted to be a feature of short gestation.

The term LBW infants had a lower mean gestational age than the controls and it might have been anticipated that the results for the term LBW group would fall between those for the preterm and control groups if "overlapping or separation" was a function of gestational age. This was not the case, however, as separation of the suture was found in excess in the term group when compared with the controls ($p < 0.005$), suggesting that growth retardation might have had a significant effect.

(iii) Length of Scalp Hair

The length of scalp hair was measured in the region above the ear. Preterm LBW infants had significantly shorter hair (less than 1 cm) than controls ($p < 0.005$) with term LBW infants falling between the two suggesting that the length of hair is related to gestational age, Table IX 4.

(iv) Appearance of Veins in the Cubital Fossa

A study was made of the appearance of the veins in the cubital fossa; this was quantitated by the degree of visibility. The high incidence of visibility of veins in the preterm infant (54/73) probably reflects an absence of subcutaneous tissue when compared with controls, of whom 124/149 lacked visible veins in the cubital fossa ($p < 0.001$), see Table IX 5. It is well known that shock causes strong vasoconstriction; this might be present in a few infants with RDS but did not appear to be an important factor.

(v) Eyelids

The appearance of the eyelids was related to gestational age in the three groups: an overall chi square analysis showed a significant difference ($p < 0.001$) between preterm LBW, term LBW and control infants, see Table IX 6. There was an excess of oedema of the eyelids in preterm LBW infants ($p < 0.001$) denoting the influence of gestation and an excess of "bagginess" amongst term LBW infants, which possibly reflects IUGR ($p < 0.01$). In a considerable excess of control infants the eyes were described as "buried" ($p < 0.001$) and this probably reflects the good nutritional state of the control infant.

(vi) Dermal Patterns

Amongst the preterm LBW infants there was an excess of - patterns (43/73) against (41/148) in control group; the number of preterm infants with + patterns present was only 15/76 compared with 54/149 for controls ($p < 0.001$), Table IX 7. Term LBW infants have an excess of + patterns (53/76) compared with 54/148 controls ($p < 0.001$) - but this probably reflects IUGR. The result reflects the effects of gestational age upon this clinical item.

The proportion of positive patterns in the term LBW group should be less than in the controls if gestational age were the only operative factor. Thus dermal patterns appear to be influenced by both gestational age and IUGR.

(vii) Condition of the Skin on the Hands

The condition of the skin on the dorsum of the hand was described as normal, dry, scaling or with the various degrees of cracking. Preterm LBW infants had a significant excess of skin described as normal (51/73) compared with controls (11/149) and all but 4 of the remainder of the preterm LBW infants were described as having dry skin (17/73) when compared with 110/149 of the controls. Cracking or scaling was present in 28/149 of the controls compared with 24/76 of the term LBW infants, see Table IX 8. There are highly significant differences (see Table IX 9) between the preterm and control groups which are presumably due to the effects of differing gestational age.

The values for term LBW infants did not fall between the preterm and control groups, suggesting that IUGR had a significant influence on the skin of term LBW babies.

(viii) Condition of the Skin Elsewhere

A similar analysis was made of the skin on the elbows, ankles, hands and feet, see Table IX 9. The condition of the skin appeared to be dependent on gestational age. There was a difference between term LBW and control groups in the condition of the skin of the dorsum ($p < 0.005$); inter-digital clefts, soles of the feet and elbows ($p < 0.025$) and dorsum of the hands ($p < 0.01$): since the distribution of the values fell between the preterm and control groups, it seems that gestational age rather than IUGR was the important determining factor.

(ix) Length of First Toe compared with the Second

In the preterm LBW group, toe length was equally distributed between shorter, longer and equal length. The patterns for term LBW and control infants were similar ($p <$ 0.[illegible]) and it was noted that the great toe was longer than the second toe in over half of all infants, see Table IX 10. There was a highly significant difference between preterm and term infants and preterm and control infants ($p < 0.005$) suggesting that gestational age was the operative factor rather than growth retardation.

(x) Oedema

Clinical oedema was present in 32/73 preterm LBW infants, 13/76 term LBW infants and 4/149 controls; the overall and individual group differences were all significant ($p < 0.001$). The distribution of oedema by situation and gestational age group is shown in Table IX 11 and it is concluded that oedema is primarily a feature of short gestation. It would be anticipated that the rate of oedema amongst term LBW infants would be slightly higher than amongst controls due to their slightly shorter mean gestation ($p < 0.001$). However, it was found that the gestational age of oedematous term LBW infants was similar to that of the non-oedematous term LBW group, thus excluding the possibility that a small group of oedematous babies with shorter gestation influenced the result.

The incidence of maternal and neonatal disease was similar in term LBW babies with and without oedema, thus excluding perinatal disease as a possible cause of oedema.

(3) Physical Characteristics affected by Intrauterine Growth Retardation

(i) Introduction

The effects of intrauterine growth retardation (IUGR) on anthropometric measurements are well documented and a number of workers have described its influence on non-anthropometric characteristics such as skin changes and subcutaneous loss in the placental dysfunction syndrome (Clifford, 1957), reduction in the size of breast tissue, and increase in the prominence of plantar skin creases

(Lubchenco, 1970), and separation of cranial sutures (Usher, 1970). During the analysis of the clinical characteristics of infants in this study, it became apparent that growth retardation affects certain characteristics. Thus it was found that some features were present in greater numbers amongst term LBW infants than amongst controls. If gestational age were the determining influence it would have been anticipated that frequency amongst term LBW infants would have fallen somewhere between preterm LBW and control infants because of the slightly shorter gestation (38.4 weeks) of the latter when compared with controls (39.7 weeks).

(ii) Methodology

The methodology of the various clinical items has already been described in the previous section with the exception of the following two items.

The size of the gastrocnemius muscle was assessed by palpation and graded as small, medium or large.

The degree of subcutaneous tissue loss over the tibia was related to the amount of skin over the anterior aspect of the tibia that could be lifted between the thumb and forefinger. Loss was scored from +++ in situations of extreme loss to -- where there was plenty of subcutaneous tissue. Clearly oedema would have a significant bearing on this clinical sign.

(iii) Sagittal Suture

There appeared to be a significant excess of sagittal suture separation amongst term LBW infants in comparison with controls, though term LBW infants had an excess of suture separation at the expense of suture approximation when compared with controls. The overall difference in the characteristics of the sagittal suture between term and control infants was statistically significant ($p < 0.005$), Table IX 3, thus IUGR influences the state of the sagittal suture.

(iv) Dermal Patterns

It has already been demonstrated that the appearance of the dermal patterns is related to gestational age. However, there was a two-fold excess of + scores amongst term LBW infants when compared with controls, which was highly significant ($p < 0.001$). It is thus concluded that IUGR significantly affects the dermal patterns (Table IX 7)

(v) Condition of the Dorsum of the Hands

The number of term LBW infants with cracking, scaling or peeling of the hands was twice that of the controls, which suggests that IUGR enhances the development of this feature (Table IX 8). A significant difference was noted for the feet and elbows (Table IX 9).

(vi) Size of Gastrocnemius Muscle

The frequency with which the muscle was described as small was similar for preterm and term LBW infants, but was very low for control infants, suggesting that growth retardation has a significant effect on the size of the muscle ($p < 0.001$), Table IX 12.

(vii) The Degree of Subcutaneous Tissue Loss over the Tibia

There is an excess of + scores for term LBW infants when compared with controls which is significant at $p < 0.001$. (Table IX 13). This strongly suggests that IUGR has a significant effect on this clinical sign.

(viii) Discussion

The physical characteristics of the newborn infant are principally related to gestational age but it is important to determine which features are also affected by IUGR. The influence of IUGR was considered to be present when the frequency of a particular item in the term LBW group did not fall between the preterm LBW and control groups, as might be expected if gestational age were the only factor.

Of the items described, two have already been reported, namely sagittal suture separation (Usher, 1970) and skin changes (Clifford, 1957). The items unique to the study were the use of dermal patterns and subcutaneous tissue loss over the tibia. The dermal pattern changes reflect both subcutaneous tissue loss and skin drying. The sign with the greatest clinical application is likely to be the degree of loss of subcutaneous tissue over the tibia; in the absence of oedema it gives a simple and useful indication of the extent of subcutaneous loss. Elsewhere, more detailed analysis of its relationship to hypoglycaemia, ponderal index and other clinical items has been undertaken. Low centile position appears to relate to tibial tissue loss whilst high positinns are related to adequate subcutaneous tibial tissue ($p < 0.005$). It would appear to be a simple clinical test to apply as a criterion of IUGR.

Conclusions

Details are presented of a number of hitherto undescribed characteristics which bear a relationship to gestational age and fetal growth.

CHAPTER X

CONGENITAL ABNORMALITIES

(1) Introduction

The association of congenital abnormalities with low birth weight and retarded fetal growth are well known, but the nature of the relationship is not fully understood. Possibly an adverse influence causing major congenital abnormality may affect fetal growth by temporary interruption of cell division, thus reducing the absolute cell number. Difficulties in assessing the effects of congenital malformation on fetal growth are increased by the problems inherent in the definition of a congenital abnormality.

Nelson and Forfar (1969) defined a major abnormality as "one which was severe enough to cause death or significant handicap" but this tells us little of the duration of the intra-uterine insult. For example, a major lesion caused by rubella acting over a period of time in utero may be quite different from the consequences of a short-acting agent, such as ergometrine used as an abortifacient. Even greater problems arise with minor abnormalities, defined as lesions unlikely to prove a serious hindrance to normal life or to the achievement of normal life expectancy (Nelson and Forfar, 1969). However, it is clear that the mechanism giving rise to certain minor abnormalities such as a single umbilical artery or palmar crease, though included with minor problems, is likely to have more serious effects on fetal growth, than a process causing such anomalies as a hydrocele or inguinal hernia.

A further difficulty associated with definition is in deciding the frequency with which a clinical finding must exist in a population to be considered abnormal. In a study of 4412 newborn infants by Marden, Smith and McDonald (1964), a condition was accepted as abnormal if it occurred in less than 4 per cent of the population. Perhaps this rather liberal definition accounts for their high congenital abnormality rate of 14.7 per cent. Yet other difficulties may be encountered in trying to assess the role played by heredity in the production of congenital abnormalities. For example, dominantly inherited cleft hand only affects the limb extremity, while the drug thalidomide can cause abnormalities of bone, malformation of the cartilages of the ear and atresia of the bowel (McBride, 1963).

(2) The Present Study

(i) Definitions

A major congenital abnormality was defined as a defect of structure or form causing a significant disability, and a minor abnormality as one unlikely to be a hindrance to normal life. Congenital abnormalities were further sub-divided according to whether the aetiological agent was likely to have caused a significant interruption in fetal growth. Thus major abnormalities, organic cardiac murmurs and hypospadias were considered likely to be associated with growth retardation while sacral sinuses, hernias, positional talipes, undescended testes and hydroceles were not. A single palmar crease is of rather debatable significance and has been included amongst those abnormalities unlikely to have a significant effect on fetal growth. Congenital dislocation of the hip (CDH) presented diagnostic problems due to the frequency of vacuum creaks and limitation of abduction on routine examination: CDH was considered to be present only when there was clear evidence of subluxation and dislocation. Though the long-term consequences can be serious, CDH was classified as a non-significant abnormality because aetiologically it is believed to be due to fetal position rather than to an interruption in embryonic development.

(ii) Results

The incidence of congenital abnormalities considered likely to produce an effect on fetal growth is shown in Table X 1. They occurred in 3.4 per cent of LBW infants (5 of 149), being more common in this group (especially among pre-term infants) than in the controls (3/149): however, the numbers were insufficient for statistical analysis. There were two syndromes (Taybi-Rubenstein and post-rubella) included under "major abnormalities" and a case of Fallot's Tetralogy under "significant cardiac murmurs". Table X 2 shows the incidence of minor congenital abnormalities thought unlikely to have a significant effect on fetal growth. They were found in 51 LBW infants (34.2 per cent) compared with 28 controls (18.8 per cent). These values are in excess of those reported in other studies but are inflated due to the inclusion of cardiac murmurs and haemangiomas which were present in the neonatal period but subsequently disappeared.

A further analysis was carried out to determine the number of times two or more "congenital abnormalities" occurred in the same infant. Three (2.0 per cent) of the LBW group were noted to have two associated abnormalities and a fourth baby had a number of abnormalities constituting the Taybi-Rubenstein syndrome; no infant with more than one abnormality was found amongst the controls. The frequency with which two or more minor congenital abnormalities occur in the same patient amongst the general population is 0.8 per cent (Smith, 1970). In the present group of LBW infants, the incidence of 2.7 per cent is more than three times this rate but is nowhere near the 15 per cent (major or three minor abnormalities) quoted by Drillien (1972). However, her figure may be higher due to the inclusion of abnormalities appearing after the neonatal period and to the fact that she considered only infants with birthweights below 2000 g.

(iii) Discussion

This investigation has been concerned with congenital abnormalities in a total surviving legitimate low birthweight population. Significant differences from other studies have been noted and three factors appear to be responsible.

(A) The definition of a major congenital abnormality has been more stringent than in a number of previous studies. In these, there has been considerable variation in interpretation of the term "congenital abnormality" and it has even been suggested that cerebral palsy (Drillien, 1964) and pyloric stenosis (McIntosh et al. 1954) should be included as congenital abnormalities. On the other hand, transient cardiac murmurs, haemangiomas and other such minor anomalies have been recorded separately in this study and this accounts for the higher rate for all congenital abnormalities noted in the newborn period (33 per cent).

(B) The age at which the abnormality is noted is very important, since up to one-fifth of congenital anomalies remain unrecognised during the first year of life (McIntosh et al. 1954).

(C) Birth weight appears to have a critical influence on the rate of congenital abnormality. A number of studies report incidences ranging from 7.5 per cent (McIntosh et al. 1954) to 15.3 per cent (Yerushalmy et al. 1965) for birth weights below 2501 g and 20.6 per cent for those below $4\frac{1}{2}$ lb (Drillien, 1964). In a study of 195 infants weighing less than 1500 g, of whom half survived, Stewart (1972) recorded that 13 per cent had recognizable structural defects apparent at birth.

There can be no doubt from these and our own studies that the rate of congenital abnormality is increased in LBW infants. However, there has been much controversy on the question of a causal relationship between impaired fetal growth and congenital abnormality. In a study of 3210 malformed fetuses with anencephaly, Down's syndrome, hydrocephaly, cleft palate and hypospadias, the first two conditions appeared to impair fetal growth significantly (Kučera and Doležalová, 1972). A number of studies show an association between IUGR and an excess of congenital abnormalities. In 180 infants with birth weights below 2000 g Drillien (1970) found an abnormality rate of 47 per cent amongst those with birth weights falling below the 10th centile. Stewart (1972) reported congenital abnormalities in four (20 per cent) of 20 surviving light-for-dates infants with birth weights below 1500 g. Yerushalmy and his colleagues (1965) noted a 7.4 per cent incidence of severe abnormalities in a study of babies delivered after 37 weeks with birth weights between 1617 and 2500 g, which was twice the rate for babies of similar weight delivered before 37 weeks.

The present study differs from those of Stewart and Drillien by including babies with birth weights up to 2500 g and by applying more stringent criteria of definition and age of diagnosis.

The incidence of major abnormalities found in the neonatal period is low in this study. Additional abnormalities found at follow-up have not been included and it is probable that more will be found with the increasing passage of time. The numbers are too small to allow conclusions to be drawn about a causal relationship between poor fetal growth and congenital abnormality in general.

(3) The Influence of Chromosomal Abnormalities on Fetal Growth

It is known that abnormalities of human chromosomes can adversely affect fetal growth. For example, Smith and McKeown (1955) reported a reduced mean birth weight in a sample of 103 cases of Down's syndrome. In a survey of 422 cases of autosomal trisomies D13 and E18 there was evidence of impaired fetal growth, partial deletion of the autosomes B4p and B5p usually lowers the birth weight whilst ring A_1 and D abnormalities seriously retard fetal growth (Chen, Chan and Falek, 1972).

Abnormalities of the sex chromosomes also affect the growth of the fetus. In a review of 147 cases of sex chromosome abnormality, Chen et al (1971), presented evidence that birth weight was reduced by aneuploidy involving the X but not the Y chromosome. Reisman (1970) noted that one third of children with Turner's syndrome were of low birth weight and were often very small for gestational age.

The depressing effect of chromosomal abnormalities on fetal growth is thus convincingly documented. However, the bias in the literature towards reporting only abnormal situations makes it difficult to determine whether chromosomal abnormalities play a significant part in the production of low birth weight in general. Wright et al (1972) reported an incidence of 5.17 chromosomal abnormalities per 1000 births and this figure has been broadly substantiated by Sergovich et al (1969) in 2, 159 consecutive newborn infants. Their figures have been directly confirmed by Ratcliff et al (1970) from a study of 3,500 consecutive newborn male infants. Anderson (1976) in a study of small-for-date infants (below 10th centile) noted that 6 out of 309 infants had major chromosomal abnormalities. Amongst term LBW infants, 5 out of 202 were noted to have chromosome abnormalities (Chen et al, 1971).

From these data it is possible to calculate the theoretical contribution of chromosomal abnormalities to low birth weight. As the LBW rate is approximately 70 per 1,000 and the chromosomal abnormality rate is 5.17 per 1,000, and assuming that all chromosomal abnormalities are manifested as LBW infants, then their maximum contribution to the phenomenon of low birth weight would be 7.4 per cent. A similar calculation can be made for the maximum contribution of chromosomal abnormalities to IUGR. If it is assumed that half the low birth weight population is growth retarded (35 per 1000) and all chromosomal abnormalities are accompanied by growth retardation, then the maximum contribution to the phenomenon of IUGR would be 14.8 per cent.

These are obviously considerable overestimates because many infants with chromosomal abnormalities are of normal birth weight. Even in well documented conditions with associated chromosomal abnormality and growth retardation, such as Turner's syndrome, only a third are of low birth weight. Taking these considerations and clinical experience into account, it seems reasonable to conclude that chromosomal abnormalities contribute less than 5 per cent towards the phenomenon of IUGR.

CHAPTER XI

NEONATAL MEASUREMENT

(1) Apgar Score

The Apgar Score (1953) has provided a useful and effective means of assessing the degree of asphyxia and need for resuscitation in the newborn infant.

It is well known that preterm LBW infants have a much higher incidence of abnormal obstetric antecedents which give rise to low scores, but the decreased muscle tone and less active response of these infants may be partly responsible for this.

Although in the past some authors have considered the Apgar score as an indicator of fetal distress, the score specifically relates to the short period just before birth. Asphyxial insults of short duration are usually reflected in the 1 minute Apgar score while asphyxia of greater length occurring prior to delivery is more likely to depress both the 1 minute and 5 minute results.

There are numerous short reports relating low Apgar scores to maternal and neonatal morbidity; the only large population study (Drage and Berendes, 1966) reported a 23 per cent mortality for Apgar scores of 0 and 1 at 1 minute and 49 per cent mortality for similar scores at 5 minutes. The study went on to relate morbidity to Apgar scores at 9 months of age, but it is not readily apparent whether an adjustment for preterm delivery was made at follow-up. Moreover, there are problems associated with a variety of examiners carrying out developmental screening of such a large cohort at nine months of age. A more recent study by Steiner and Neligan (1975) of 22 babies who showed perinatal cardiac arrest reported a very satisfactory outcome as long as active rapid resuscitation was initiated and the baby established regular active respiration within 30 minutes after the heart beat had been restored. Beyond the 30 minute period the prognosis was extremely gloomy, and of the four such babies, all developed severe cerebral palsy.

More detailed study of the work of Drage and Berendes (1966) shows that a low Apgar score (0 - 3 at 1 minute) carries a 3.6 per cent neurological abnormality rate and a similar Apgar score at 5 minutes carries a 7.4 per cent abnormality rate at one year of age. The abnormality rate in a total population of 14,115 babies was 1.9 per cent.

There is little doubt that use of the Apgar score has made a significant contribution to the resuscitation of newborn infants; however, major difficulties result if attempts are made to use the score to quantitate the duration of asphyxia.

(i) Methodology

In the present study, Apgar scores were obtained in all babies except two preterm LBW infants. One of these was born before arrival and the second was born in the ambulance, but arrived in time for the 5 minute score to be assessed.

(ii) Results

As might be anticipated there was an excess of low scores amongst the index population when compared with the controls. In all, 11.4 per cent of controls and 32.3 per cent of LBW infants had scores below 6 at 1 minute; there was an excess of preterm infants in the LBW group (Table XI.1). At 5 minutes of age, 6.1 per cent of LBW infants had values below 6 compared with 0.7 per cent of controls (Table XI 2). For the 1 and

5 minute scores there was a highly significant difference ($p < 0.001$) between the means of the total LBW and control infants (see Tables XI 3 and XI 4).

The 1 and 5 minute scores for preterm LBW infants were significantly different when compared with the term LBW group ($p < 0.05$ and $p < 0.01$ respectively).

The incidence of low Apgar scores, particularly amongst preterm LBW infants, seem rather high by present day standards and suggests that recent advances in obstetrics care may be having a significant impact, particularly on the management of preterm infants.

(2) Mode of Delivery

Analysis of the mode of delivery for each baby in the study showed a significant excess ($p < 0.001$) of caesarean section and forceps delivery amongst the total LBW group (see Table XI 5). When comparing preterm and term LBW infants, the mode of delivery was broadly similar in both groups (Table XI 6).

(3) Blood Pressure

The measurement of blood pressure in the neonate is a sadly neglected clinical investigation. In any other age group, routine and indeed frequent blood pressure measurements would be carried out. The failure to assess the blood pressure in the neonate is usually attributed to the technical difficulty and lack of co-operation by the patient. As the newborn infant is particularly vulnerable to hypotension and the recent work of Hambleton and Wigglesworth (1976) relates intraventricular haemorrhage to rupture of the capillaries in the germinal layer following a rise in arterial blood pressure in association with hypoxia or hypercapnia, routine estimation of neonatal blood pressure seems long overdue.

A variety of methods has been used, including digital palpation, the flush method, arterial pulsation and direct arterial measurements. The mean neonatal systolic blood pressure at term has been reported as 74 mmHg in a group of 74 white infants (Schachter et al, 1976). Considerably lower values have been recorded for preterm infants, ranging from 35 mmHg at 23 weeks of gestation to 65 mmHg at 36 weeks (Goodman, Cumming and Raber, 1962). Direct intra-aortic measurements of blood pressure in 74 term infants gave values of 72 mmHg SD 10 and 47 mmHg SD 7 for systolic and diastolic pressures respectively. Lower values were found in 26 preterm infants, 64 mmHg SD 10 and 39 mmHg SD 8 for systolic and diastolic pressures respectively. Blood pressure in the neonate is related to time of feeding, thermal stress and tilting of the infant (Bordiuk and Keitel, 1973).

The systolic blood pressure was measured in all babies in the present study by the method of Ashworth, Neligan and Rogers (1959). The measurements were made during the first few days of life - usually between 12 and 36 hours of age - in triplicate, 2-3 hours after a feed. Satisfactory readings were obtained in almost all cases; when the baby was not co-operative, restlessness was allayed by inducing the baby to suck the examiner's finger.

(i) Results

The distribution of systolic blood pressure for the sample is shown in Table XI 7. Only a small proportion of control (7.4 per cent) had systolic blood pressure values equal to or below 60 mmHg, compared with 57.5 per cent of preterm LBW and 31.6 per cent of term LBW infants. The mean value for control infants was 69.1 mmHg, SD 6.2 which is significantly higher ($p < 0.001$) than those for the total LBW infants at 60.6 mmHg, SD 8.9; the preterm LBW infants at 58.0 mmHg SD 8.2; and the term LBW infants at 63.7 mmHg, SD 6.0. There was a significant difference between preterm and term LBW infants ($p < 0.001$). Such results might be anticipated in view of the weight and gestation of the groups under study (see Table XI 8).

In preterm infants, low blood pressure was associated with an increased incidence of low 5 minute Apgar scores ($p < 0.05$), and a positive Silverman score recording ($p < 0.02$). Amongst term LBW infants, the only condition associated with a low neonatal blood pressure was a depressed 5 minute Apgar score ($p < 0.01$).

The distribution of systolic blood pressure in the sample is shown in Table XI 7; 14 LBW infants had values below 51 mmHg; only one of these infants was at term. Control infants showed a higher distribution of systolic pressures, 6 infants having values over 80 mmHg.

A more detailed study of systolic blood pressure values below 51 mmHg was made in 13 preterm infants. The mean values for the groups were:- birth weight, 1587.6g SD 355.5g; gestational age 31.3 SD 2.9 weeks; centile position 32.5; ponderal index 2.2 SD 0.16; Apgar scores 5.2 and 7.2 at one and five minutes. A surprisingly high mean blood glucose value of 58.8 mg (74 individual readings) probably represents the effects of intravenous feeding. One term LBW infant had a blood pressure falling below 51 mmHg.

Of the small group of preterm babies with low systolic blood pressure a significant proportion had birth weights below 1500 g (7) and were delivered prior to 33 weeks' gestation (10). This might be anticipated, knowing the difficulties that such babies may encounter. However, there was a small group of slightly heavier babies (6) greater than 1500 g and of longer gestational age (3) which suggests that a very small number of babies cannot maintain an adequate blood pressure; such infants may have serious long-term developmental problems.

The poor prognosis associated with a low systolic blood pressure (below 40 cm, of water) was documented by Hall and Oliver (1971). Five out of 18 infants receiving volume expanders survived, compared with 0 out of 19 untreated patients with blood pressures below 40 cm of water ($p < 0.05$).

As early as 1934, Londe reviewed the literature as well as estimating the blood pressure in 78 premature infants. There has been relatively little interest in the subject since that date, and yet the devastating effects of hypotension in causing death and disability make such measurement mandatory. However, further knowledge must be gained concerning the normal values found in the neonate: of particular interest is the association of low blood pressure with very low birth weight. It is clear that the LBW infant is capable of surviving low systolic blood pressures, but the actual level of blood pressure tolerated clearly deserves more detailed study from the points of view both of immediate survival and long-term development.

(4) Blood Glucose

Many authors have related symptomatic hypoglycaemia to impaired long-term development and intellectual performance. The pathological studies carried out by Anderson, Milner and Strich (1967) described extensive nerve cell degeneration throughout the CNS in prolonged hypoglycaemia. It is now widely recognised that asymptomatic transient hypoglycaemia is very unlikely to be associated with neurological damage (Griffiths and Bryant, 1971). As part of the present study, an attempt was made to elucidate the long-term effects of hypoglycaemia by a prospective trial and to weigh the relative contributions of such factors as birth asphyxia, a raised packed cell volume, and an adverse social background as causative factors in reduced IQ of babies with impaired fetal growth.

(i) Methodology

It was decided to measure blood glucose levels on average seven times during the first 72 hours in low birth weight infants, and on three occasions at 24 hourly intervals in controls. At the time when the study was planned, measurement of blood glucose was quite widely carried out by the use of chemical methods which estimated the amount of reducing substance in the blood. A pilot study was undertaken to determine the blood glucose level by methods employing reduced substances (Hoffman, 1937), as well as by enzymic methods using glucose oxidase (Morley, Dawson and Marks, 1968). A mean of 52.9 mg SD 14.9 per 100 ml was obtained for the former, compared with 40.8 mg SD 11.2 for the latter, the statistical difference being highly significant ($p < 0.001$), indicating the inaccuracy of the reducing substance method.

(ii) Results

The mean blood glucose values - excluding cases on intravenous therapy - for controls in 430 readings was 57.4 SD 12.0 mg per 100 ml. For preterm infants in 447 readings it was 53.7 SD 25.6 mg per 100 ml. This appears to be slightly higher than for term LBW infants which in 505 readings was 50.7 SD 28.0 mg per 100 ml, despite the longer gestation of the latter but there is not as great a difference as might be anticipated in view of the known affects of IUGR.

Of the control infants, only 1 had all three values below 30 mg per 100 ml, which falls within the hypoglycaemic range as defined by Cornblath et al (1966). On the other hand in 9 low birth weight infants, 21 readings were below 20 mg per 100 ml which is defined as hypoglycaemia by Cornblath et al (1966). Three infants had repeated values below 20 mg per 100 ml. Of the 9 LBW infants with glucose values below 20 mg per 100 ml, 8 were below the 10th centile, the mean ponderal index was 2.8 SD 0.24 which was much higher than anticipated. 6 of the 9 infants were preterm, thus hypoglycaemia seems to be a significant problem within this group.

It was a clinical impression during the study that blood glucose values rose with increasing age. To test this hypothesis correlation coefficients were calculated for blood glucose values in relation to age. There was only a marginal increase in blood glucose values over the first 72 hours as reflected by regression analysis. Correlation coefficients of + 0.28 for controls and + 0.22 for total

LBW and + 0.32 for preterm LBW and + 0.19 for term LBW and the results are shown in Table XI 9.

(iii) Conclusions

Detailed estimation of blood glucose values were obtained during the study and it is planned to relate the mean and lowest blood glucose values to IQ at subsequent follow-up. Initial data from the 9 month follow-up does not show an association of delayed development with a low blood glucose value. However, the effects of hypoglycaemia may only be apparent on IQ and such observations would have to await the results of the long term follow-up.

(5) Jaundice

The degree of jaundice was estimated clinically on a daily basis in all infants and the bilirubin estimation was carried out where the clinical information suggested a level above 12 mg per cent. In those cases where the bilirubin was estimated by laboratory methods the mean value in total LBW was 13.8 mg SD 4.0, preterm LBW 14.1 mg SD 4.0 and term LBW 13.3 SD 3.8, there being no significant differences between the groups.

Serum bilirubin levels associated with kernicterus (above 20 mg per cent) were found in 5 LBW infants of which 4 were preterm and 1 at term. More recently it has been the practice to exchange preterm LBW infants at a lower level, in those infants with uncomplicated perinatal histories 18 mg per cent is widely used and lower levels - 16 depending upon the number of complications. Bilirubin values between 18 and 20 mg per cent were found in 5 LBW infants, (3 preterm LBW and 2 term LBW) and bilirubin levels between 16 mg and 18 mg per cent were found in 11 LBW infants of which 9 were preterm LBW.

High bilirubin levels were analysed against the 9 month follow-up data and failed to demonstrate any association with delayed development or hearing loss. As with hypoglycaemia the effects of hyperbilirubinaemia may effect parameters not capable of detection at 9 months of age.

(6) Packed Cell Volume

The capillary packed cell volume (PCV) was estimated on two occasions during the initial neonatal period. The mean value for controls in 232 readings was 60.8 SD 8.9 with preterm LBW infants 59.8 SD 13.2 in 131 readings and slightly higher value in term LBW infants 61.5 SD 13.0 in 144 estimation. Extremes of haematocrit (equal to or above 70 per cent) occurred in 32 LBW, 11 preterm LBW and 21 term LBW. Low values (< 50 per cent) were found in 17 low birth weight of which 12 were preterm and 5 term LBW. This compares with 11 control infants with a similar value.

A study was made of the change in PCV with increasing age. The rise found between 24 and 48 hours found in previous studies did not occur in this sample. However, there were much fewer estimations carried out between 24 and 48 hours of age; the reason for this discrepancy is not apparent. A drop of 15 per cent from the first PCV reading to the second one (usually estimated on the third day) occurred in 9 LBW (5 preterm and 4 term) compared with 1 control. Conversely, a rise of 15 per cent in PVC occurred in 1 term LBW and 1 control.

There appear to be a greater variation in the first and second haematocrit amongst LBW infants compared with controls. This may be due either to initial deydration in term infants or through loss of blood through sampling. It is likely that a number of preterm infants had significant amounts of blood taken for investigatory purposes.

Extremes of packed cell volume will not appear to be associated with abnormal development as seen at 9 months of age.

Conclusions

The results of a variety of neonatal measurements are presented and their importance relates to their possible association with long term developmental handicap. It is tacitly assumed that low Apgar scores (≤ 5), blood glucose (≤ 20 mg), hypotension (≤ 50 mmHg) and high bilirubin (≥ 16 mg) and packed cell volume ($\geq 70\%$) are regularly implicated in long term handicap. Examination of the nine months follow-up data fails to demonstrate a significantly greater association with any one item. The association of at least two of these abnormal parameters in any one baby was studied. The most common association amongst preterm LBW (7) was a low Apgar score and an elevated bilirubin. Amongst term LBW (4) the predominant combination was a low Apgar score and blood glucose. There did not appear to be a greater incidence of handicap amongst these 17 LBW infants at 9 months follow-up.

CHAPTER XII

MORBIDITY FROM ONE MONTH TO FOUR YEARS OF AGE IN LOW BIRTH WEIGHT INFANTS AND THEIR MATCHED CONTROLS

(1) Introduction

There have been numerous reports about the consequences of low weight at birth but surprisingly few on morbidity from unrelated conditions. Certain difficulties became apparent on attempting to study morbidity in early childhood. For example, the child has a natural susceptibility to illness which diminishes as immunity is acquired; the average child may have between six to eight respiratory infections in any one year (Williams and Phelan, 1975). The definition of illness can create serious methodological difficulties; Miller et al (1960) used the following definition: "Any condition sufficient to produce constitutional disturbance or alteration of behaviour in the child or concern in the parent". Drillien (1964) defined illness as evidence of definite pathology or constitional disturbance as a result of which the child received medical or hospital attention. She sometimes included children from poorer homes when significant constitutional symptoms were present but medical aid had not been sought.

The morbidity data of Ven den Berg (1968) are probably the most accurate available: she analysed the records of a group of children participating in a pre-paid health programme and found the incidence of disease in the second year of life amongst LBW infants to be 3.8 illnesses per year compared with 3.5 for those infants with a birth weight over 2500 g. As the families were using the scheme for their medical care, this is likely to have been an accurate reflection of the incidence of disease requiring medical attention.

Another approach has been the use of health visitors to identify the incidence of disease (Douglas and Mogford, 1953; Drillien, 1964). In Douglas and Mogford's study, a significant excess of hospital admission was recorded for infants weighing less than 5 lbs over controls weighing more than $5\frac{1}{2}$ lbs. However, if diseases associated with prematurity were excluded the rates of hospital admission were very similar, with the exception of admissions for lower respiratory disorders like bronchitis and pneumonia. The major reservations about this national survey were the reliance on a large number of health visitors and the dependence upon maternal memory.

(2) Morbidity in the Present Study

In the present study, data from the Royal Aberdeen Children's Hospital were used as criteria of disease or illness. Since the hospital with its associated casualty department is the only one serving the entire area, it is reasonable to assume that the data are representative of the incidence of disease requiring referral to hospital in those children still resident in the area. The casualty data are likely to under-represent the incidence of minor emergencies because children who have moved out from the city centre are more likely to be taken to their general practitioner for minor injuries. Referral to a casualty department will only be made in these circumstances when there are specific requirements such as X-ray. The rate of migration from Aberdeen and its suburbs is very low compared with other areas such as the London boroughs, and although some sample loss occurred it was not a serious problem in the present series.

The hospital in-patient, out-patient and casualty records were analysed separately when each child reached four years of age.

There were such records for 48 preterm LBW infants, 38 term LBW infants and 58 control infants in the sample.

(i) Diseases recorded

(A) Central Nervous System Disorders

There is an excess of delayed development, cerebral palsy, convulsions and strabismus amongst LBW infants, as shown in Table XII.1. Preterm LBW infants feature prominently amongst those with strabismus and delayed development. Two term LBW infants displayed delayed development manifested recognisable syndromes associated with retardation (Epiloia and Taybi - Rubenstein Syndrome). Despite the small numbers, there was a significant excess of preterm and term LBW infants with convulsions compared with controls ($p < 0.001$).

(B) Gastro-Intestinal Disorders

Nine LBW infants had inguinal or umbilical hernia compared with one control (Table XII.2). This higher rate amongst LBW infants may represent a genetic predisposition or may be a result of the less satisfactory growth that takes place after birth in babies delivered before term. Hospital admissions for diarrhoea and vomiting occurred more frequently amongst LBW infants and this may in part represent less satisfactory environmental conditions.

(C) Ear, Nose and Throat Conditions

The operation of tonsillectomy either alone or with adenoidectomy was performed on fourteen LBW infants as shown in Table XII.3. One control infant was subjected to this procedure. No social class bias was noted (SC II - 2; IIIa - 1; IIIb - 4; IV - 1; V - 4).

Enlargement of tonsillar and adenoidal tissue is a natural response to infection. As LBW infants suffer from an increased number of infections, removal of these structures is irrational. It is likely that the general anxiety surrounding LBW infants impels parents towards physical solutions to their worries.

(D) Social and Psychiatric Problems

In the LBW group there were rather more social and psychiatric problems and more children who ingested noxious materials (Table XII.4). This finding was anticipated in the light of the known increase in social pathology amongst LBW infants.

The children were assessed at a maximum age of four years, too early to consider enuresis as an index of impaired child-rearing. However, there already appears an excess of referrals for enuresis amongst the LBW group.

(E) Trauma

Children from socially deprived backgrounds tend to have a higher incidence of injury. Table XII.5 indicates the various types of trauma with the anticipated excess of LBW infants. The observation that more LBW infants were the victims of non-accidental injury is another index of the adverse environment of LBW infants.

(F) Skin Disorders

The increased incidence of napkin dermatitis and scabies (Table XII.6) is not surprising and reflects the lower level of hygiene amongst LBW infants.

(G) Orthopaedic Conditions

The high referral rate for congenital dislocation of the hip in the LBW group (22.1 per cent) and to a lesser extent amongst controls (8.7 per cent) seen in Table XII. 7 compares with the rate of 0.4 per cent for normal population. These values probably reflect the incidence of vacuum clicks and variations in abduction which subsequently proved to be benign. All cases were referred at four weeks of age and were treated by orthopaedic surgeons. The excessive rate of congenital dislocation of the hip appearing in the Children's Hospital notes reflects referral by junior staff and should be compared with the lower rate of diagnosis report by the survey staff (see Table X.2)

(H) Respiratory Infections

The slightly increased incidence of respiratory infections amongst LBW infants does not reach statistical significance.

(I) Miscellaneous Conditions

There were 38 other diseases recorded amongst the LBW infants compared with 26 in controls (Table XII.8) The data indicate a preponderance of condition considered as serious in LBW group: the term infants continue to contribute heavily towards morbidity.

(ii) Casualty Records

An assessment was made of the casualty attendance up to the age of four years of all children still residing within the area. Attendances were divided into categories based on the major presenting feature. Ingestion of a noxious substance presented few problems in definition, but where a fall had occurred involving injury to the head it was classified under head injury. Lip and mouth injuries were included under head injury.

Analysis of the results (Table XII.9) shows no significant difference between the various categories, though it might have been expected that LBW infants, because of their social background, would show a higher attendance rate. It is known that males have a higher incidence of trauma and disease than females and the sex ratio of casualty attendance ($p < 0.05$) in this study bears this out (Table XII.10).

There was a small group of children who visited casualty on four or more occasions. Indeed one control child was brought up on thirteen occasions. There was an excess of female children ($p < 0.01$) in this small group (Table XII.11) but no social class gradient was demonstrated.

(3) Discussion

In the present sample, hospital records existed for 86 LBW infants and 58 controls, the difference being statistically significant ($p < 0.005$). When casualty records were examined there were 77 for LBW infants compared with 79 for controls; there was a significant excess of males in both LBW and control groups.

The anticipated excess of conditions directly attributed to low weight at birth was noted in the present study. Neurological disorders were virtually confined to LBW infants: the low rates for cerebral palsy and developmental delay are broadly in agreement with recently reported surveys. However, these are not strictly comparable with the present study as they have dealt with groups either of infants with very low weight at birth (Rawlings, et al, 1971) or of infants who were light-for-dates at term (Fitzhardinge and Steven, 1972). Furthermore, these studies were based on hospital rather than geographical populations and differences in their findings may in part be due to selection factors.

In the present study, there was a greater incidence of anaemia and hernia and a marked excess of tonsillectomy and adenoidectomy in the LBW population when compared with control infants. Despite careful matching for social factors, there was a high incidence of environment - related conditions such as ingestion, fractures, trauma and child abuse amongst the LBW children. When comparing the rates of miscellaneous disease, there were no significant differences either in the number or the degree of severity.

Examination of the casualty records showed a significant excess of males, both LBW and controls, attending casualty when compared with females. However, the total numbers of visits were similar in the control males, LBW males and females. The finding of a similar attendance rate for female LBW children is due to the small excess of female LBW attenders with more than four casualty visits. The attendances of female control infants were significantly less than those of the other three groups.

Conclusions

The morbidity pattern between one month and four years of age is described. It shows a higher incidence of disease amongst low birth weight infants. Detailed analysis of casualty records shows a significant excess of low birth weight infants attending the casualty department when compared with infants of normal weight at birth.

SUMMARY AND CONCLUSIONS

Chapter I CHANGING PATTERN OF CARE OF THE NEWBORN INFANT

The literature on recent therapeutic advances in the care of the newborn infant is reviewed. Major advances have taken place in the management of asphyxia, apnoea attacks, infection, disorders of bilirubin metabolism, haemolytic disease, hypoglycaemia, nutritional disorders, respiratory distress and temperature variations.

In some instances, therapeutic advances have been at a heavy clinical cost. Examples are the inappropriate use of certain antibiotics in the neonate, the initial failure to appreciate the adverse effects of using vitamin K, and the excessive use of oxygen therapy.

Knowledge in certain areas appears to have lagged: in particular, our understanding of intracranial haemorrhage, blood pressure and the appropriate management of hyperviscosity. There have been several outstanding technical advances, such as the use of exchange transfusion, intravenous alimentation and the management of respiratory distress syndrome. Each of these is likely to be superseded in time by simpler measures such as the use of anti-D, nasojejunal feeding and improved general management of labour and the early neonatal period.

Chapter II LOW BIRTH WEIGHT

The methodological problems associated with previous studies of LBW are reviewed by detailed analysis of published work.

The fallacies of definitions which ignore gestation, and of using different standards of birth weight, race and geographical area are stressed. The importance of controls and the advantages of using random, sibling and matched controls are fully discussed.

Methodological problems during assessment at follow-up, such as age at examination, sample loss, the use of intelligence tests, the influence of the environment, and the use of statistics, are discussed. The lack of neonatal biochemical data and the failure to define intrauterine growth retardation are emphasised.

The major findings of the more important earlier studies are described.

1. The improvement in mortality rates is noted.
2. The physical growth of LBW infants does not reach that of their peers.
3. A higher incidence of chronic handicap amongst LBW infants was noted during the 1950's and early 60's.
4. Intelligence was impaired with a disturbingly high incidence of low I.Q. More recent studies have shown a dramatic improvement in the overall morbidity.
5. The intellectual sequelae of impaired fetal growth indicate an overall slight reduction in intellectual performance compared with the normal grown fetus.
6. The poorer environment of LBW infants is repeatedly confirmed in successive studies.

From this review of previous studies, major methodological problems are apparent. A prospective study must be based on a clearly defined population with matched controls, and should record environmental information as well as perinatal physical and biochemical data.

Chapter III PLAN OF THE PRESENT STUDY

1. The sample consisted of 149 legitimate singleton LBW infants delivered in Aberdeen and its conurbation between the 1st July 1969 to 30th June 1970.

2. Controls (birth weight > 2,500 gms) were prospectively matched for social class, ordinal position, maternal height and smoking habits and the sex of the infant.

3. Controls were accurately matched in 86 pairs. Difficulty was experienced in selecting controls due to the stringent criteria: maternal height was the criterion most usually relaxed. Overall an improvement in matching for height was achieved allowing 2" difference rather than using broad categories.

Methodological details are outlined for the various clinical measurements used during the study. The physical appearance, estimation of menstrual age, anthropometric measurement, statistical analysis, biochemical details and data handling are outlined in detail.

Chapter IV MATERNAL CONTRIBUTION TO LOW BIRTH WEIGHT

In this chapter, maternal characteristics of LBW infants and their matched controls were compared in detail.

When birth weight was adjusted for maternal height, the mean addition for low birth weight was 63.9 g SD 140.4 compared with 24.9 g SD 113.7 for controls.

When birth weight was adjusted for maternal height and mid-pregnancy weight, the mean addition was 88.2 g SD 164.9 for total LBW, 107.4 g SD 149.8 for term LBW and 14.7 g SD 150.6 for control infants.

Maternal smoking patterns showed an excess of heavy smokers before pregnancy and in the first half of pregnancy amongst mothers of LBW infants. Fathers of LBW infants showed a significant excess of heavy smokers.

There were fewer first pregnancies amongst the LBW group than amongst the controls.

Social class was well matched between the LBW group and their controls. However, the incidence of low social class in the present study was over one and a half times the rate found in the general population.

Maternal disease associated with pregnancy occurred in 108 instances amongst the LBW group compared with 49 instances amongst controls. Maternal disease not specifically related to pregnancy was recorded in 101 mothers of LBW compared with 76 controls.

The latter part of the chapter reviews the literature and discusses the influence on fetal growth of maternal nutrition, illegitimacy and psycho-social factors. From the evidence presented, all three appear to have a significant influence on fetal growth.

Chapter V DEFINITION OF INTRAUTERINE GROWTH RETARDATION

1. This chapter compares eight different methods of defining IUGR.

   I The merit of using weight for gestational age as a means of defining fetal growth is discussed. The use of such a method is unquestioned but one must be aware of the limitations.

   II The relative merits of using birth weight, occipito-frontal circumference, crown-heel length, ponderal index and birth weight adjusted for maternal height were analysed. For the controls these anthropometric measurements were equally effective in identifying infants with impaired fetal growth. Amongst LBW infants a very different pattern emerged. For birth weight, there was an excess of infants with low centile positions but this was not found for occipito-frontal circumference, crown-heel length and ponderal index. Depending upon the anthropometric measurement used, rather different patterns of impaired fetal growth emerge.

III A statistical comparison was made of the centile distribution for the various anthropometric measurements. The controls showed a similar population distribution for each of the anthropometric measurements, except for occipito-frontal circumference. The LBW group showed similarities for all anthropometric measurements except birth weight and ponderal index. Preterm LBW infants showed similar distributions except for crown-heel length and ponderal index. Amongst term LBW infants there was a significant difference for most anthropometric measurements against birth weight.

IV The definition of fetal growth by use of an arbitrary percentage reduction in the mean birth weight is discussed. Further analysis shows it to be an unsatisfactory method of defining fetal growth, due to the exponential rate of fetal growth.

V The use of anthropometric ratios in the definition of fetal growth is discussed: neither the ponderal index nor the occipito-frontal circumference to crown-heel ratio was found to be more helpful than other methods.

2. Fetal growth was classified by comparing the relative centile positions for birth weight, occipito-frontal circumference and crown-heel length. Each baby was arbitrarily classified as fat, thin, long, short or appropriate. Despite the potential of this method, it was no more successful in identifying babies with IUGR.

3. A group of infants was identified as showing severe growth retardation (below - 2 SD for gestation - Gruenwald and Minh, 1961). Despite the use of a stringent definition, there was no difference in the maternal and neonatal biological characteristics when compared with a group defined by less vigorous criteria.

4. A cluster analysis programme utilising over 200 items was used to generate individual sub-groups of infants. A detailed statistical analysis was carried out when six individual sub-groups of infants had been identified. As might be expected, the control population was homogenous. The total low birth weight population demonstrated the effects of gestational age, with a small sub-group clustering at 30 weeks, a larger group at 34 and three separate groups at term. Further analysis of the low birth weight group confirmed the influence of short gestation. Amongst the term LBW infants two groups of infants were identified with extremes of clinical characteristics, namely those of normal inf nts delivered at 37 weeks showing reasonable nutrition and, at the opposite extreme, a group which demonstrated severe clinical evidence of growth retardation.

5. The use of individual maternal and neonatal physical and morbidity characteristics did not result in the identification of sub-groups of infants. It may be that such sub-groups exist, but may not be apparent in a sample of this relatively small size. The various methods of defining intrauterine growth retardation are discussed. To date it does not appear that a satisfactory clinical definition has been described.

Chapter VI SIBLINGS OF LBW INFANTS

1. A search was made of the Aberdeen Maternity Hospital records for birth histories of siblings: siblings of 116 LBW infants (242 pregnancies) and 118 controls (203 pregnancies) were traced.

2. The outcome of pregnancy was considered in a number of categories:

   i Preterm LBW deliveries were associated with a higher rate of abortions in other pregnancies (22.2%).

   ii Preterm LBW IUGR deliveries appeared to be a sporadic event.

   iii Term IUGR LBW deliveries have a 23.3% chance of a similar occurrence in another pregnancy and this may reach 27.6% when preterm IUGR live births are included.

   iv Controls infants were assumed to be normally grown; despite an excess of maternal smoking, lower social class and shorter stature when compared with the general population, the siblings of control infants had a lower incidence of preterm and growth retarded delivery.

3. Characteristics of LBW infants were studied where two or more LBW infants occurred in a sibship. Despite a very detailed examination of maternal and neonatal characteristics, no differences were found in this group when compared with the total LBW population.

Chapter VII THE SIGNIFICANCE OF GESTATIONAL AGE

1. Gestational age is considered to be the simplest indicator of maturity and a review of the literature highlights some of the difficulties.
2. 61.1% of the LBW group and 65.8% of controls were of certain gestational age. No significant differences were found in the mean gestational age between certain and uncertain groups except for preterm LBW infants.
3. Morbidity patterns are related to gestational age to act as a yardstick for further analysis.
   As morbidity patterns were similar for certain and uncertain categories, they were combined in subsequent analyses.

Chapter VIII THE CONFIRMATION OF GESTATIONAL AGE BY EXTERNAL PHYSICAL CHARACTERISTICS (TOTAL MATURITY SCORE)

1. The various methods of corroborating gestational age are outlined. The total maturity score (TMS) was

utilised in the study to confirm the date of the LMP and to assess the accuracy of the TMS as a means of estimating gestational age.

2. The TMS was calculated for all but one infant and all but thirteen infants were studied within the recommended time period. It was fundamental to the study that the examiner did not know the length of gestation as stated by the mother.
3. Inter-observer reliability showed a difference between the two observers but this was not thought to be significant in clinical terms.
4. Comparison of the difference between the TMS and LMP showed significant differences for preterm LBW infants, which was consequently reflected in the results for the total LBWs. A possible explanation for the results may be due to the structure of the TMS at short gestational ages. The controls were noted to have a significant difference (0.3 weeks) but this is thought to be unimportant in clinical practice.
5. It is concluded that the use of the TMS is justifiable as a means of calculating gestatinnal age but it becomes progressively less reliable as the duration of gestation shortens.
6. There is a detailed discussion of both the literature and problems in the use of TMS as a method of corroborating gestational age.

Chapter IX PHYSICAL CHARACTERISTICS, GESTATIONAL AGE AND GROWTH

The association of non-anthropometric characteristics to gestational age and the influence of fetal growth is analysed in this chapter. The items of the total maturity score were shown to relate to gestation rather than to the effects of IUGR. A number of additional non-anthropometric physical items were assessed. Overlapping of the saggital sutures, short length at scalp hair, visible veins in the cubital fossa, oedema of the eyelids, dermal skin patterns, normal skin texture and oedema are primary features of short gestation. Saggital suture separations, dermal skin patterns, cracking, scaling and peeling of the hands, small size of the gastrocnemius muscle and loss of subcutaneous tissue over the tibia, were all significantly associated with intrauterine growth retardation.

Chapter X CONGENITAL ABNORMALITIES

The contribution of congenital and chromosomal abnormalities to the production of LBW is reviewed. The rate of incidental congenital abnormalities is high amongst LBW infants (34.2%) compared with 18.8% of controls. The rate of abnormalities thought to be significant in the production of impaired fetal growth was 3.4% for the LBW group and 2% for controls. The association of two or more abnormalities was only found in 2% of LBW infants.

The literature on the relationship of chromosomal abnormalities to the production of LBW is reviewed in the second section. From theoretical considerations, chromosomal abnormalities are calculated to occur in less than 5% of LBW infants, which compared with a rate of 2% reported in the literature.

Chapter XI NEONATAL MEASUREMENT

A variety of neonatal parameters are discussed in this chapter. The distribution of apgar scores below 6 at 1 and 5 minutes was 11.4% for controls and 32.3% for LBW infants and 0.7% of controls and 6.1% of LBW infants respectively. The incidence of low scores, particularly amongst preterm LBW infants seems rather high by present day standards and suggests that recent advances in obstetric management may be having a significant impact.

Mode of delivery was analysed and showed a significant excess of caesarean section and forceps delivery amongst the total LBW group.

The distribution of systolic blood pressure is also described, a few controls (7.4%) had values below 60 mmHg compared with 57.5% of preterm LBW and 31.6% of term LBW.

Blood glucose levels were estimated 7 times during the first 72 hrs of LBW infants and on 3 occasions at 24 hourly intervals in controls. The glucose level for controls was 57.4 SD 12.0 mg, for preterm infants 53.7 SD 25.6 mg and for term LBW 50.7 SD 28.0 mg per 100 ml.

Biliburin levels were estimated to quantitate clinical jaundice and 5 LBW had values over 20 mg per cent and a further 5 had values between 18 and 20 mg.

Packed cell volume was estimated on 2 occasions during the initial neonatal period. The mean value for controls was 60.8 SD 8.9 and in preterm LBW infants 59.8 SD 13.2 and in term LBW 61.5 SD 13.0. Extremes of haematocrit ≥ 70% occurred in 32 LBW infants while low values (< 50%) were found in 17 LBW infants.

Chapter XII MORBIDITY FROM ONE MONTH TO FOUR YEARS

The morbidity pattern was studied using hospital records of those children aged from one month to four years of age who attended the RACH. Details were obtained for 86 LBW and 58 control infants. The anticipated excess of CNS disorders was noted. The poor social background of LBW infants was reflected in the higher incidence of gastrointestinal disorders, psychiatric problems and trauma. There was a significant excess of tonsillectomies amongst the LBW group (14) compared with controls (1).

Casualty records were also analysed. The number of visits was similar for control male infants and LBW male and female infants. Control female infants did not attend casualty as frequently as the other three groups. There was a small group of children (19) who attended casualty on 4 or more occasions and, within this group there was an excess of female infants.

MAJOR CONCLUSIONS

This study has shown that the use of a clearly defined, ethnically homogeneous population will obviate a number of serious methodological difficulties which have been inherent in virtually all previous studies. The prospective nature of the study made it possible to collect a wide variety of biological data - particularly biochemical information - which will be of considerable relevance in long-term follow-up.

The use of carefully matched controls enabled specific comparisons to be made, which have indicated important differences between low birth weight infants and their controls. Thus it has been clearly shown that low birth weight infants have a significantly inferior socio-biological background. This fact has rarely been taken into account when assessing the outcome of low birth weight in relation to management.

The demonstration that matched controls may differ significantly in a variety of ways should stimulate both interest and future research. There is a tendency to assume that advances in perinatal technology will result in further improvements in the subsequent progress and later intelligence of low birth weight infants. While this may prove to be correct, greater attention might more profitably be directed towards removing some of the differences shown to exist between low birth weight infants and their matched controls. Possible areas of improvement would be in the maternal environment as well as in maternal nutrition, smoking habits and fertility.

It was hoped in this study to refine the current definitions of impaired fetal growth. Despite studying eight different methods, it proved impossible to arrive at a satisfactory clinical definition. This was due, at least in part, to the diversity of influences which operate to impair fetal growth. Inability to achieve a suitable definition applicable to the newborn infant has important implications. Thus, for example, the currently used statistical definition embraces a heterogeneous population, the components of which may have significantly different intellectual and physical outcomes. As it has not been possible to define fetal growth retardation satisfactorily during extra-uterine life, it seems unlikely that a suitable intra-uterine description will be feasible in the near future.

TABLE III 1

Low Birth Weight Cohort

(Singleton births, Aberdeen and Conurbation

1st July 1969 - 30th June 1970)

Total births	198
Deaths	23
Rejected	26
Missed	3
Refused	1
Available to Sample	145*

*In addition, 4 babies born after this period were studied. These infants have been included in the population study.

TABLE III 2

Rejected Babies

Illegitimate	12
Staff	4
Armed Forces	3
Students	3
Emigrated	2
Widow	1
Non Caucasian	1
Total	26

TABLE III 3

Social Class

Social Class	Controls	%	Total LBW	%	Aberdeen City *		%
I	10	6.7	10	6.7	I	457	8.1
II	16	10.7	11	7.4	II	702	12.5
IIIa	9	6.0	12	8.1	IIIa	594	10.6
IIIb	35	23.5	29	19.5	IIIb	1403	25.0
IIIc	21	14.1	25	16.8	IIIc	839	15.0
IV	26	17.4	30	20.1	IV	873	15.6
V	32	21.5	32	21.5	V	613	10.9
					N.S.	130	2.3
Total	149		149			5611	

*Data obtained from Aberdeen Maternity Hospital 1969-70.

TABLE III 4

Ordinal Position in Family

	Controls	%		Total LBW	%
1	79	53.3	1	78	52.3
2	40	26.8	2	36	24.2
3	21	14.1	3	26	17.4
4	3	2.0	4	3	2.0
5	4	2.7	5	2	1.3
6	1	0.7	6	1	0.7
7	1	0.7	7	1	0.7
			8	1	0.7
			9	1	0.7

TABLE III 5

Distribution by Maternal Height

	Controls		Total LBW		Aberdeen *	
Maternal Height	No.	%	No.	%	No.	%
Small	48	32.2	65	43.6	1258	22.4
Medium	71	47.6	58	38.9	2631	46.9
Tall	30	20.1	26	17.4	1709	30.5
Not known	0		0		13	0.2

Maternal Height of Controls	mean	157.5 cm	(SD 5.2 cm)
Maternal Height of Total LBW	mean	156.0 cm	(SD 6.3 cm)
Maternal Height - City	mean	158.1 cm	(SD 5.8 cm)

* Derived from all married legitimate singleton births 1969-70 (City and Suburbs of Aberdeen)

TABLE III 6

Maternal Smoking Habits

Controls

Cigarettes per day	Pre-pregnancy	First 20 weeks	Last 20 weeks
None	55	63	62
Light ≤ 10	45	34	31
Moderate 11 - 20	41	39	38
Heavy ≥ 21	6	11	16
Not recorded	2	2	2

Total LBW

Cigarettes per day	Pre-pregnancy	First 20 weeks	Last 20 weeks
None	52	54	56
Light ≤ 10	37	32	22
Moderate 11 - 20	40	38	42
Heavy ≥ 20	14	19	23
Not recorded	6	6	6

TABLE III 7

Birth Weight by Sex - Total LBW

Grams	Males	Females	Total
700 - 1000	0	2	2
1001 - 1250	1	2	3
1251 - 1500	1	7	8
1501 - 1750	6	6	12
1751 - 2000	15	6	21
2001 - 2250	14	15	29
2251 - 2500	37	37	74

TABLE III 8

Matching Characteristics

(Of the 149 case and controls, 86 pairs were correctly matched.

The table shows the categories of the remainder)

	Incorrect	Relaxed	Totals
Smoking	5	6	11
Height	12	25	37
Ordinal position	1	6* 2+	9
Class	0	5 1*	6
Sex	0	0	0
Total	0	0	63

* "grand multip" of any parity considered as para 4

\+ para 2 + 3 used interchangeably

TABLE III 9

Distribution of Birth Weight

Controls		Total LBW	
Grams	No.	Grams	No.
2501 - 2750	16	700 - 1000	2
2751 - 3000	24	1001 - 1250	3
3001 - 3250	31	1251 - 1500	8
3251 - 3500	32	1501 - 1750	12
3501 - 3750	21	1751 - 2000	21
3751 - 4000	20	2001 - 2250	29
4001 - 4250	4	2251 - 2500	74
4251 - 4500	1		

TABLE III 10

Gestational Age Distribution

	Controls			Total LBW		
Weeks of age	Certain	Uncertain	Total	Certain	Uncertain	Total
27	0	0		1	1	2
28	0	0		2	1	3
29	0	0		5	0	5
30	0	0		3	0	3
31	0	0		1	2	3
32	0	0		4	3	7
33	0	0		9	3	12
34	0	1	1	6	0	6
35	0	0		6	12	18
36	0	0		7	7	14
37	2	2	4	9	8	17
38	11	9	20	14	10	24
39	20	10	30	15	8	23
40	44	16	60	5	3	8
41	20	9	29	4	0	4
42	1	4	5	0	0	0
Total	98	51	149	91	58	149

Controls - Mean Gestational Age
280.3 days (SD 8.4)

Total LBW - Mean Gestational Age
254.2 days (SD 22.5)

TABLE III 11

Examiner - General Examination

Examiner	Control	Total LBW	Total	%
Not recorded	0	1	1	0.3
J.I.C.	118	124	242	81.2
E.J.D.	31	24	55	18.4

TABLE III 12

External Physical Characteristics in the Estimation of

Gestational Age

	Controls	Total LBW	Total	%
Not examined	0	1	1	0.3
Examined by J.I.C.	121	122	243	81.5
Examined by E.J.D.	28	26	54	18.1

TABLE III 13

Neurological Examination in the Estimation of Gestational Age

	Controls	Total LBW	Total	%
Not examined	9	50	59	19.7
Examined by J.I.C.	94	10	104	34.5
Examined by E.J.D.	46	89	135	45.3

TABLE III 14

Anthropometric Measurements - J.I.C.

	Controls	Total LBW	Total	% Examined
OFC	118	125	243	81.5
Crown Heel	128	133	261	87.5
Crown Rump	128	133	261	87.5
Thoracic circumference	119	125	244	81.8
Skinfold Thickness	123	127	250	83.8

TABLE III 15

Comparison of OFC Measurements between Examiners

Source	Ssqs	d.f.	MSq	F	
Subjects	298.9040	15	19.9269	2758.0484	S
Doctors	0.0791	1	0.0791	10.9481	S
Interaction	0.2628	15	0.0175	2.422	N/S at 1%
Residual	0.2312	32	0.0072		
Total	299.4771	63			

TABLE III 16

Comparison of Crown-Heel Measurements between Examiners

Source	Ssqs	d.f.	MSq	F
Subjects	58.3930	5	11.6786	763.3072
Doctors	0.0035	1	0.0035	0.2289
AM/PM	0.1335	1	1.1335	8.7255
Subject-Doctor Interaction	1.1473	5	0.2295	15.0000
Subject-AM/PM Interaction	1.2640	5	0.2528	16.5229
Doctor-AM/PM Interaction	0.1512	1	0.1512	9.8824
Subject-Doctor-AM/PM Interaction	0.6230	5	0.1246	8.1438
Residual	0.7333	48	0.0153	
Total	62.4488	71		

TABLE III 17

Comparison of Crown-Rump Measurements between Examiners

Source	Ssqs	d.f.	MSq	F
Subjects	53.4017	5	10.6803	1136.2021 s.
Doctors	15.1250	1	15.1250	1609.0426 s.
AM/PM	1.5606	1	1.5606	166.0213 s.
Subject-Doctor Interaction	0.7700	5	0.1540	16.3830 s.
Subject-AM/PM Interaction	7.2077	5	1.4415	153.3511 s.
Doctor-AM/PM Interaction	0.1422	1	0.1422	15.1277 s.
Subject-Doctor-AM/PM Interaction	0.6395	5	0.1279	13.6064 s.
Residual	0.4533	48	0.0094	
Total	79.3000	71		

TABLE III 18

Comparison of Thoracic Circumference between Examiners

Source	Ssqs	d.f.	MSq	F
Subjects	640.5529	14	45.7538	1837.5020 s.
Doctors	0.0360	1	0.0360	1.4458 n.s.
Interaction	1.3907	14	0.0993	3.9880 s.
Residual	1.4933	60	0.0249	
Total	643.4729	89		

TABLE III 19

Comparison of Skinfold Thickness Readings Between Examiners

Source	Ssqs	d.f.	MSq	F	
Subjects	174398.4375	23	7582.5408	567.2116	s.
Doctors	7014.0625	1	7014.0625	524.6866	s.
Interaction	2265.1042	23	98.4828	7.3670	s.
Residual	1283.3333	96	13.3681		
TOTAL	184960.9375	143			

TABLE IV 1

Number of Infants with Birth Weight Adjusted for Maternal Height

Birth Weight	Controls	%	Total LBW	%	Preterm LBW	%	Preterm IUGR	%	Term LBW	%
Increased	89	59.7	99	66.4	44*	60.3	14	77.8	55*	72.4
Same	0		0		0		0		0	
Reduced	60	40.3	48	32.2	28	38.4	4	22.2	20	26.3
No information	0		2	1.3	1	1.3	0		1	1.3
TOTAL	149		149		73		18		76	

*Preterm LBW v Term LBW $p < 0.025$

TABLE IV 2

Mean Birth Weight Adjustment for Maternal Height

	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW
Mean birth weight adjustment	+24.9 g	+63.9 g	+54.0 g	+78.9 g	+70.5 g
Standard deviation (SD)	113.7 g	140.4 g	148.8 g	135.2 g	133.0 g

Total LBW cf Controls $p < 0.01$

Preterm IUGR cf Controls NS

Term LBW cf Controls $p < 0.02$

TABLE IV 3

Number of Babies with Birth Weight Adjustment for Maternal Height and Mid Pregnancy Weight

Birth Weight	Controls	%	Total LBW	%	Preterm LBW	%	Preterm IUGR	%	Term LBW	%
Increased	71	47.6	98	65.8	44	60.3	13	72.2	54	71.0
Same	0		1	0.7	0		0		1	1.3
Reduced	58	38.9	40	26.8	23	31.5	4	22.2	17	22.4
No information	20	13.4	10	6.7	6	8.2	1	5.6	4	5.3
TOTAL	149		149		73		18		76	

Significance

Total LBW	v	Controls	$p < 0.001$	
Preterm LBW	v	Term LBW	$p < 0.05$	
Preterm LBW	v	Controls	$p < 0.1$	NS
Term LBW	v	Controls	$p < 0.001$	

TABLE IV 4

Mean Birth Weight Adjustment for Maternal Height and Mid Pregnancy Weight

	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW
Mean Birth Weight Adjustment	14.7 g	88.2 g	67.5 g	109.4 g	107.5 g
Standard Deviation (SD)	150.6 g	164.9 g	177.4 g	135.5 g	149.8 g

Total LBW	cf	Controls	$p < 0.001$
Preterm LBW	cf	Term LBW	$p < 0.25$
Preterm LBW	cf	Controls	$p < 0.05$
Term LBW	cf	Controls	$p < 0.001$
Preterm IUGR	cf	Controls	$p < 0.01$

TABLE IV 5

Comparison of Maternal Smoking Patterns Between LBW and Control Mothers

Maternal smoking patterns	pre-pregnancy phase				First 20 weeks				Last 20 weeks				Significance with increasing gestation
	Control	%	Total LBW	%	Control	%	Total LBW	%	Control	%	Total LBW	%	
Non Smoker	55	36.9	52	34.9	63	42.3	54	36.2	62	41.6	56	37.6	NS
Light Smoker (≤ 10)	45	30.2	37	24.8	34	22.8	32	21.5	31	20.8	22	14.8	NS
Moderate Smoker (11 - 20)	41	27.5	40	26.8	39	26.2	38	25.5	38	25.5	42	28.2	NS
Heavy Smoker (≤ 21)	6	4.0	14	9.4	11	7.4	19	12.8	16	10.7	23	15.4	NS
Not Recorded	2	1.3	6	4.0	2	1.3	6	4.0	2	1.3	6	4.0	NS
Significance	$p < 0.005$				$p < 0.05$				$p < 0.1$ NS				

TABLE IV 6

Father's Smoking Pattern

	Controls	%	Total LBW	%	Preterm LBW	%	Preterm IUGR	%	Term LBW	%
Non Smoker	44	29.5	43	28.9	22	30.1	6	33.3	21	27.6
Light (≤ 10)	33	22.1	18	12.1	11	15.1	2	11.1	7	9.2
Moderate (11-20)	44	29.5	44	29.5	18	24.7	4	22.2	26	34.2
Heavy (≤ 21)	15	10.1	24	16.1	14	19.2	5	27.8	10	13.2
Not Recorded	8	5.4	17	11.4	8	10.9	1	5.6	9	11.8
Pipe	5	3.4	3	2.0	0		0		3	4.0
TOTAL	149		149		73		18		76	

Total LBW and Controls $p < 0.01$

TABLE IV 7

Pregnancy Number

Pregnancy Number	Controls	%	Total LBW	%	Preterm LBW	%	Preterm IUGR	%	Term LBW	%
1	70	47.0	57	38.3	26	35.6	6	33.3	31	40.8
2	41	27.5	40	26.8	16	21.9	6	33.3	24	31.6
3	19	12.8	28	18.8	16	21.9	0		12	15.8
4	9	6.0	9	6.0	4	5.5	3	16.7	5	6.6
5	1	0.7	7	4.7	4	5.5	0		3	4.0
6	7	4.7	3	2.0	2	2.7	1	5.6	1	1.3
7	2	1.3	3	2.0	3	4.1	0		0	
8	0		1	0.7	1	1.4	1	5.6	0	
9	0		1	0.7	1	1.4	1	5.6	0	
TOTAL	149		149		73		18		76	

TABLE IV 8

Pregnancy Number - Significant Results

Pregnancy 1 compared second and subsequent pregnancy		Pregnancy 1 compared third and subsequent pregnancy		Pregnancy 1 compared fourth and subsequent pregnancy	
Total LBW cf Controls	$p < 0.05$	Total LBW cf Control	$p < 0.025$	Total LBW cf Controls	$p < 0.05$
		Preterm LBW cf Control	$p < 0.005$	Preterm LBW cf Control	$p < 0.025$
				Preterm LBW v Term LBW	$p < 0.025$

TABLE IV 9

Social Class

RG Social Class	Controls	%	Total LBW	%
I	10	6.7	10	6.7
II	16	10.7	11	7.4
IIIa	9	6.0	12	8.1
IIIb & c	56	37.6	54	36.2
IV	26	17.4	30	20.1
V	32	21.5	32	21.5
TOTAL	149		149	

TABLE IV 10

Maternal Disease Associated with Pregnancy

	Controls	%	Total LBW	%	Significance	Preterm LBW	%	Term LBW	%	Significance
PET and Hypertension	21	14.1	35	23.5	$p < 0.05$	18	24.6	17	22.4	NS
Placenta Praevia	0		5	3.4	NS	4	5.5	1	1.3	NS
Antepartum Haemorrhage	0		3	2.0	NS	3	4.1	0		NS
Other APH	4	2.7	23	15.4	$p < 0.001$	11	15.1	12	15.1	NS
Haemorrhage < 28 weeks	24	16.1	42	28.2	$p < 0.025$	23	31.5	19	25.0	NS
"Maternal Disease" (Total)*	49	32.9	108	72.5		59	80.8	49	64.5	NS
Total Cases	149		149			73		76		

*Mothers where one or more pregnancy diseases occurred

TABLE IV 11

Maternal Disease Unassociated with Pregnancy

	Controls	%	Total LBW	%	Preterm LBW	%	Preterm IUGR	%	Term IUGR	%
Endocrine	3	2.0	4	2.7	2	2.7	0		2	2.6
TB	4	2.7	3	2.0	2	2.7	2	11.1	1	1.3
Heart Disease	7	4.7	4	2.7	1	1.4	1	5.6	3	3.9
Anaemia	2	1.3	6	4.0	3	4.1	1	5.6	3	3.9
Urinary Tract Infection	21	14.1	22	14.8	12	16.4	2	11.1	10	13.2
CNS Disease										
Gynaecological	0		11	7.4	7	9.6	0		4	5.3
Shirodker Suture	0		5	3.4	3	4.1	1	5.6	2	2.6

TABLE IV 12

The Combined Incidence of Maternal Disease Occurring Prior to and During Pregnancy

	Controls	%	Total LBW	%	Preterm LBW	%	Preterm IUGR	%	Term LBW	%
Disease associated with pregnancy	45	30.2	79	53.0	44	60.3	13	72.2	35	47.9
Disease unassociated with pregnancy	32	21.5	35	23.5	22	30.1	9	50.0	13	17.1
Individuals with any disease conditions	76	51.0	100	67.1	56	76.7	15	83.3	44	57.9
Individuals without any disease conditions	73	49.0	49	32.9	17	23.3	3	16.7	32	42.1
TOTAL	149		149		73		18		76	

TABLE V 1

Comparison of the Population Distribution for Centile Position by Birth Weight, Occipito-Frontal Circumference, Crown-Heel Length and Ponderal Index for Controls

	Birth Weight	Occipito-Frontal Circumference	Crown-Heel Length	Ponderal Index
Birth Weight	0	0	0	0
Occipito-Frontal Circumference	$p < 0.01$	0	0	0
Crown-heel Length	NS	$p < 0.001$	0	0
Ponderal Index	NS	NS	NS	0

TABLE V 2

Comparison of the Population Distribution for Centile Position by Birth Weight, Occipito-Frontal Circumference, Crown-Heel Length and Ponderal Index for Total LBW

	Birth Weight	Occipito-Frontal Circumference	Crown-Heel Length	Ponderal Index
Birth Weight	0	0	0	0
Occipito-Frontal Circumference	$p < 0.001$	0	0	0
Crown-Heel Length	$p < 0.001$	NS	0	0
Ponderal Index	$p < 0.001$	$p < 0.01$	$p < 0.001$	0

TABLE V 3

Comparison of the Population Distribution for Centile Position by Birth Weight, Occipito-Frontal Circumference, Crown-Heel Length and Ponderal Index for Preterm LBW

	Birth Weight	Occipito-Frontal Circumference	Crown-Heel Length	Ponderal Index
Birth Weight	0	0	0	0
Occipito-Frontal Circumference	NS	0	0	0
Crown-Heel Length	NS	NS	0	0
Ponderal Index	NS	NS	$p < 0.005$	0

TABLE V 4

Comparison of the Population Distribution for Centile Position by Birth Weight, Occipito-Frontal Circumference, Crown-Heel Length and Ponderal Index for Term LBW

	Birth Weight	Occipito-Frontal Circumference	Crown-Heel Length	Ponderal Index
Birth Weight	0	0	0	0
Occipito-Frontal Circumference	NS	0	0	0
Crown-Heel Length	NS	$p < 0.005$	0	0
Ponderal Index	NS	$p < 0.005$	$p < 0.001$	0

TABLE V 5

Ponderal Index

Ponderal Index	Controls	Total LBW	Preterm LBW	Term LBW
≤ 2.0	1	5	2	3
2.1	1	8	5	3
2.2	2	17	11	6
2.3	2	26	15	11
2.4	7	18	9	9
2.5	20	33	11	22
2.6	25	12	6	6
2.7	18	13	5	8
2.8	25	3	1	2
2.9	21	2	0	2
3.0	13	0	0	0
3.1	6	1	1	0
3.2	4	1	1	0
3.3	0	1	1	0
Unrecorded	4	9	5	4
TOTAL	149	149	73	76
Mean	2.69*	2.43*	2.40	2.4
SD	0.29	0.23	0.25	0.20

significance $^{*}p < 0.001$

TABLE V 6

OFC/CH % Distribution

	Controls		Total LBW		Preterm LBW		Term LBW	
	Number	%	Number	%	Number	%	Number	%
85	0		1		0		1	1.3
80	1	0.7	1	0.7	1	1.4	0	
78	0		0		0		0	
77	0		1	0.7	1	1.4	0	
76	3	2.0	1	0.7	0		1	1.3
75	0		3	2.0	1	1.4	2	2.6
74	7	4.6	8	5.4	5	6.8	3	3.9
73	12	8.1	15	10.1	4	5.5	11	14.4
72	14	9.4	21	14.1	11	15.1	10	13.1
71	20	13.5	30	20.1	14	19.2	16	21.0
70	34	22.9	19	12.8	10	13.6	9	11.8
69	20	13.5	12	8.1	5	6.8	7	9.2
68	18	12.2	19	12.8	9	12.3	10	13.1
67	9	6.1	7	4.7	5	6.8	2	2.6
66	5	3.4	1	0.7	1	1.4	0	
65	1	0.7	1	0.7	1	1.4	0	
60	1	0.7	0		0		0	
0	4	2.7	9	6.7	5	6.8	4	5.3
Mean	0.70		0.71		0.71		0.71	
SD	0.25		0.26		0.26		0.26	

TABLE V 7

Distribution of Sample Defined as Fat, Thin, etc, Where Centile Position Differs by at Least one Position

	Controls	%	Total LBW	%	Preterm LBW	%	Term LBW	%
Long	13	8.7	8	5.4	2	2.7	6	7.9
Short	37	24.8	14	9.4	13	17.8	1	1.3
Fat	9	6.0	13	8.7	12	16.4	1	1.3
Thin	22	14.8	36	24.2	10	13.7	26	34.2
Big head	28	18.8	28	18.8	6	8.2	22	28.9
Small head	12	8.1	12	8.1	11	15.1	1	1.3
Appropriate	24	16.1	29	19.5	14	19.2	15	19.7
Not known	4	2.7	9	6.0	5	6.8	4	5.3
TOTAL	149		149		73		76	

TABLE V 8

Distribution of Sample Defined as Fat, Thin, etc, Where Centile Differs by at Least One Position

	Controls	%	Total LBW	%	Significance
Long	13	8.7	8	5.4	NS
Short	37	24.8	14	9.4	$p < 0.001$
Fat	9	6.0	13	8.7	NS
Thin	22	14.8	36	24.2	$p < 0.05$
Big head	28	18.8	28	18.8	NS
Small head	12	8.1	12	8.1	NS
Appropriate	24	16.1	29	19.5	NS
Not known	4	2.7	9	6.0	NS
TOTAL	149		149		

TABLE V 9

Distribution of Sample Defined as Fat, Thin, etc, Where Centile Differs by at Least One Position

	Controls	%	Preterm LBW	%	Significance
Long	13	8.7	2	2.7	NS
Short	37	24.8	13	17.8	NS
Fat	9	6.0	12	16.4	$p < 0.025$
Thin	22	14.8	10	13.7	NS
Big head	28	18.8	6	8.2	$p < 0.05$
Small head	12	8.1	11	15.1	NS
Appropriate	24	16.1	14	19.2	NS
Not known	4	2.7	5	6.8	NS
TOTAL	149		73		

TABLE V 10

Distribution of Sample Defined as Fat, Thin, etc, Where Centile Differs by at Least One Position

	Controls	%	Term LBW	%	Significance
Long	13	8.7	6	7.9	NS
Short	37	24.8	1	1.3	$p < 0.001$
Fat	9	6.0	1	1.3	NS
Thin	22	14.8	26	34.2	$p < 0.001$
Big head	28	18.8	22	28.9	NS
Small head	12	8.1	1	1.3	NS
Appropriate	24	16.1	15	19.7	NS
Not known	4	2.7	4	5.3	NS
TOTAL	149		76		

TABLE V 11

Distribution of Sample Defined as Fat, Thin, etc, Where Centile Differs by at Least One Position

	Preterm LBW	%	Term LBW	%	Significance
Long	2	2.7	6	7.9	NS
Short	13	17.8	1	1.3	$p < 0.001$
Fat	12	16.4	1	1.3	$p < 0.005$
Thin	10	13.7	26	34.2	$p < 0.005$
Big head	6	8.2	22	28.9	$p < 0.005$
Small head	11	15.1	1	1.3	$p < 0.01$
Appropriate	14	19.2	15	19.7	NS
Not known	5	6.8	4	5.3	NS
TOTAL	73		76		

TABLE V 12

Distribution of Sample Defined as Fat, Thin, etc, Where Centile Position Differs by at Least Two Positions

	Controls	%	Total LBW	%	Preterm LBW	%	Term LBW	%
Long	3	6.1	0	0	0	0	0	0
Short	19*	38.7	3*	8.6	2	15.3	1	4.5
Fat	0	0	2	5.7	2	15.3	0	0
Thin	11*	22.4	19*	54.3	4	30.6	15	68.2
Big head	9	18.4	5	14.3	0	0	5	22.7
Small head	7	14.3	6	17.1	5	38.4	1	4.5
Appropriate	0	0	0	0	0	0	0	0
TOTAL	49		35		13		22	

*$p < 0.005$

TABLE V 13

Height Distribution of Mothers with a Severely Growth Retarded Fetus

Maternal Height (cm)	Number	%
< 155	15	45.5
155 - 162	14	42.4
> 162	3	9.1
Unrecorded	1	3.0
TOTAL	33	

TABLE V 14

Birth Weight Adjustment (grams) for Stature in Mothers with a Severely Growth Retarded Fetus

	Severe IUGR	SD	Term LBW - Severe IUGR	SD	Significance
Mean birth weight adjustment for maternal height	+ 68.8	128.8	+ 66.1	131.7	NS
Mean birth weight adjustment for maternal height and midpregnancy weight	+ 95.5	134.1	+112.0	160.6	NS

TABLE V 15

Smoking Characteristics of Mothers with a Severely Growth Retarded Fetus

					Cigarettes per day			
	Non Smoker	%	≤ 10	%	11 - 20	%	≥ 20	%
Pre-pregnancy	14	42.4	6	18.2	7	21.2	5	15.2
First trimester	16	48.5	4	12.1	7	21.2	5	15.2
2nd trimester	15	45.5	4	12.1	6	18.2	7	21.2

Unknown = 1

TABLE V 16

Control Cluster Analysis

	G1	G2	G4	G6	G8	G13	Extremes where significance is in excess of
Number	16	41	25	11	39	17	
Gestational age mean	39.4	38.9	39.4*	40.5*	39.7	39.9	*p < 0.001
Birthweight mean	3282	3476	2999*	3475*	3277	3278	*p < 0.001
Occip. Frontal circumference mean	34.5	34.9	34.3*	35.6*	34.3*	34.7	*p < 0.02
Crown-heel mean	49.71	49.9	48.8*	50.4*	48.8*	49.7	*p < 0.02
Total maturity score	26.8	25.4	22.4*	28.6*	25.5	27.8	*p < 0.001
(TMS in weeks)	40.7	40.4	39.5	41.0	40.5	40.9	
Abortions	3/16	6/41	6/25	0/11	5/39	1/17	NS
Maternal disease	6/16	12/41	11/25	6/11	7/39	3/17	NS
Haem. < 28/52	3/16	7/41	3/25	1/11	8/39	3/17	NS
Uncertain dates	4/16	13/41	12/25	3/11	12/39	7/17	NS
Sex	13 ♂	38 ♂	13 ♂	10 ♂	38 ♂	16 ♂	
Centile position (< 10)	3/16	1/41	4/25	2/11	3/39	1/17	NS
Mean glucose (mg)	56.7	56.8	54.1	52.2	59.2	62.3	NS
Social class (1+2)	2/16	5/41	5/25	1/11	9/39	3/17	NS
Pregnancy (1st)	5/16	22/41	10/25	6/11	18/39	9/17	NS
Smoking	9/16	19/41	13/25	6/11	29/39	10/17	NS
Dehydration	3/16	0/41	0/25	1/11	7/39	3/17	NS
Ponderal index	2.7	2.8	2.6	2.7	2.8	2/17	NS
Growth retardation index	2.1	1.4*	1.3*	3.5*	2.7	2.1	*p < 0.001

TABLE V 17

Total Low Birth Weight Cluster Analysis

	G1	G2	G4	G5	G7	G93+	Extremes where significance is in excess of
Number	43	37	24	16	26	3	
Gestational age mean	37.5	36.3	38.4	30.6*	34.1	32.0	*p < 0.001
Birthweight mean	2276	2235	2234	1374*	2084*	1546	*p < 0.05
Occip. Frontal circumference	32.3	31.6	32.1	27.2*	31.1*	NR	*p < 0.01
Crown-heel mean	45.7	44.9	45.3	38.7*	44.0*	NR	*p < 0.05
Crown-rump mean	29.7	29.0	29.4	25.3*	28.8	NR	*p < 0.001
Total Mat. Score	22.2	16.9*	21.8	8.5*	16.6*	10	*p < 0.001
(TMS in weeks)	39.5	37	39.3	31.2	36.8	32.4	
Descript. of eyes				Oedema			p < 0.05
Scalp veins	Visible				Absent		p < 0.01
Thickness of subcut. tissue	Moderate loss	slight loss	moderate loss	severe loss	Normal		p < 0.01
Subcut. tibial loss	+ (++)	+	+++	-+	-		p < 0.025
Dehydration	Minimal		Minimal				p < 0.025
Skin at micro level	*++	+	++*	-	+-		*p < 0.01
Skin on trunk	Cracking	Peeling	Peeling	Normal	Normal		
Skin at joints	Cracking	Cracking	Cracking	Normal	Normal		p < 0.05
Sagittal suture	Separated	Separated	Separated	Overlap	Overlap		p < 0.05
Growth retard. index	3.3*	2.0	4.3*	1.1	1.4		*p < 0.02
Weight gest. centile mean	5th	5th	5th	25th	25th		p < 0.025
Smoking	32/43	19/37	19/24	10/16	0/26		*p < 0.05
IV therapy	5/43	3/37	0/24	12/16*	10/26		*p < 0.005
PET	7/43	14/37*	8/24*	0/16	5/26		*p < 0.025
Sex	43 ♂	33 ♂	23 ♂	13 ♂	23 ♂	2 ♂	
Resp. distress	4/43	4/37	0/24	11/16*	11/26		*p < 0.001

+G93 - Not included in statistical analysis

<u>TABLE V 18</u>

<u>Preterm LBW Cluster Analysis</u>

	G1	G2	G6	G9	G30	+G41	Extremes where significance is in excess
Number	16	26	14	9	5	3	
Gestation mean	34.2	32.8	30.9*	35.2	35.6	32.0	*p < 0.05
Birthweight mean	2080	1993	1497*	2249	2150	1546	*p < 0.001
Occipit. frontal circumference mean	31.1	30.6	27.8*	31.9	31.8	NR	*p < 0.001
Crown-heel mean	44.1	43.3	40.1*	44.7	45.8	NR	*p < 0.05
Crown-rump mean	28.7	28.1	26.1*	29.1	29.2	NR	*p < 0.01
Total maturity score	15.8	14.1	9.0*	21.1	21.4	10	*p < 0.05
(TMS in weeks)	36.3	35.3	31.6	39.0	39.1	32.4	
Eyes			Oedema*				*p < 0.05
Scalp veins	Visible	absent	absent				p < 0.05
Sex	16 ♀	♂ 25	♀ 12	♂ 8	3 ♀	2 ♂	
Skin fold (cm)	0.38*	0.35	0.30*	0.28*	0.35	NR	*p < 0.01
IV therapy	4/16	9/26	10/14*	0/9	0/5	2/3	*p < 0.005
Resp. distress	5/16	11/26	9/14	0/9*	0/5	0/3	*p < 0.01
Growth retardation index	1.8	1.6	0.8	1.7	4.8*	1.0	*p < 0.05
Low apgar	4/16	12/26	9/14	1/9*	1/5	1/3	*p < 0.05
Glucose mean (mg)	53.8	54.9	55.6	45.5	47.6	86.4	p < 0.02

+ (G 41) not included in statistical analysis

TABLE V 19

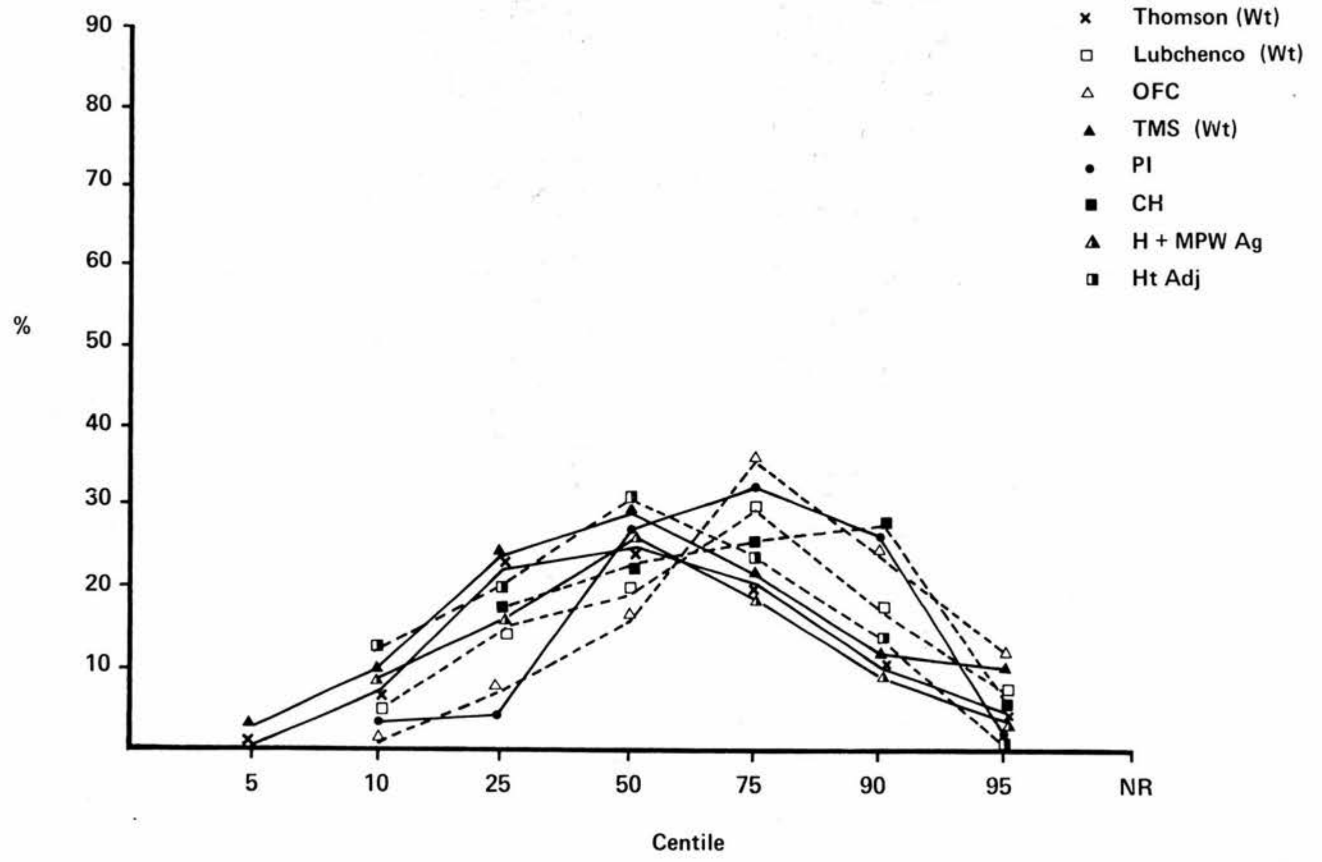
Term LBW - Cluster Analysis

	G1	G2	G3	G4*	G23	G25	Extremes where significance is in excess of
Number	14	23	11	1	10	17	
Gestation mean	38.4	38.2	38.4	38.0	39.4*	38.1	$p < 0.05$
Birthweight mean	2289	2224	2265	740	2370	2369	NS
Occip. frontal circumference mean	32.1	32.3	31.9	25.3	32.6	31.9	NS
Crown-heel mean	45.4	45.7	45.4	29.8	45.6	45.4	NS
Total mat. score	20.6	22.2	22.2	15.0	24.6	17.5*	$p < 0.05$
(TMS in weeks)	38.7	39.5	39.5	35.6	40.2	37.4	
Appearance of eyes	Oedema					normal	$p < 0.005$
Scalp veins	absent	visible*			absent	absent	*$p < 0.025$
Skin on trunk	cracking	cracking	peeling		superficial peeling	normal	*$p < 0.05$
Skin micro level		+,++				- ±	$p < 0.05$
Subcut. tissue	normal	loss*				normal	*$p < 0.001$
Tibial loss	normal	+,++, +++				normal	
Hydration	normal	dehydration			dehydration	normal	$p < 0.025$
Oedema index	9/14	2/23	2/11		0/10	2/17	$p < 0.005$
Ponderal index	2.5	2.3*	2.4		2.5	2.5	$p < 0.01$
Maternal smoking	7/14	19/23	7/11	0	7/10	8/17	$p < 0.025$
Sex	13 0	21 0	0 11	0*	9 0	0 16	
Blood glucose mean (mg)	51.3	47.4	55.1	(20.8)	51.1	56.6	$p < 0.001$
Mean skin fold (cm)	0.4*	0.3*	0.34*	0.25	0.34	0.42	$p < 0.001$
Growth retardation index	2.4	4.4*	3.9	3	3.8	1.9	$p < 0.001$

* Not included in statistical analysis

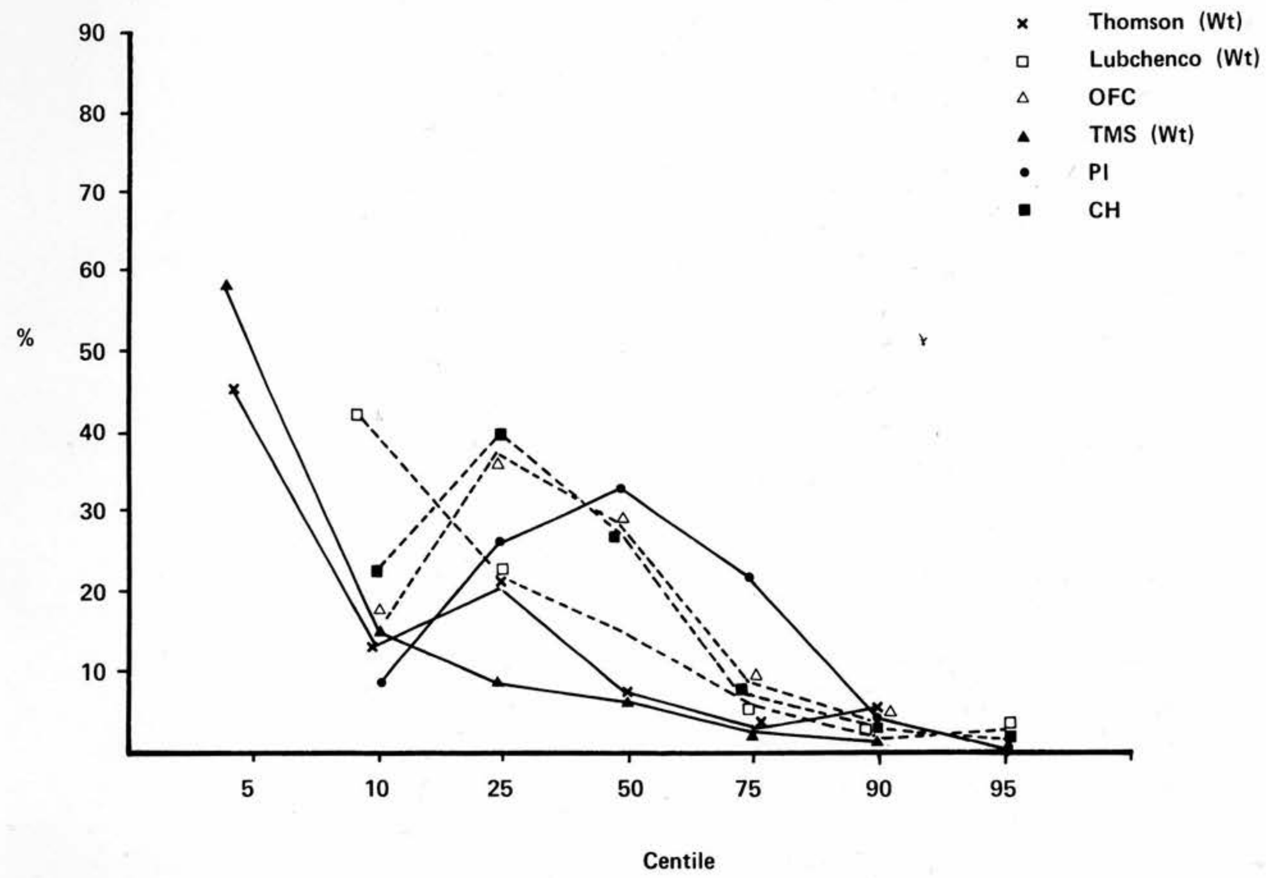
Graph V 1

CENTILE DISTRIBUTION BY SEPARATE DEFINITION
TOTAL CONTROLS



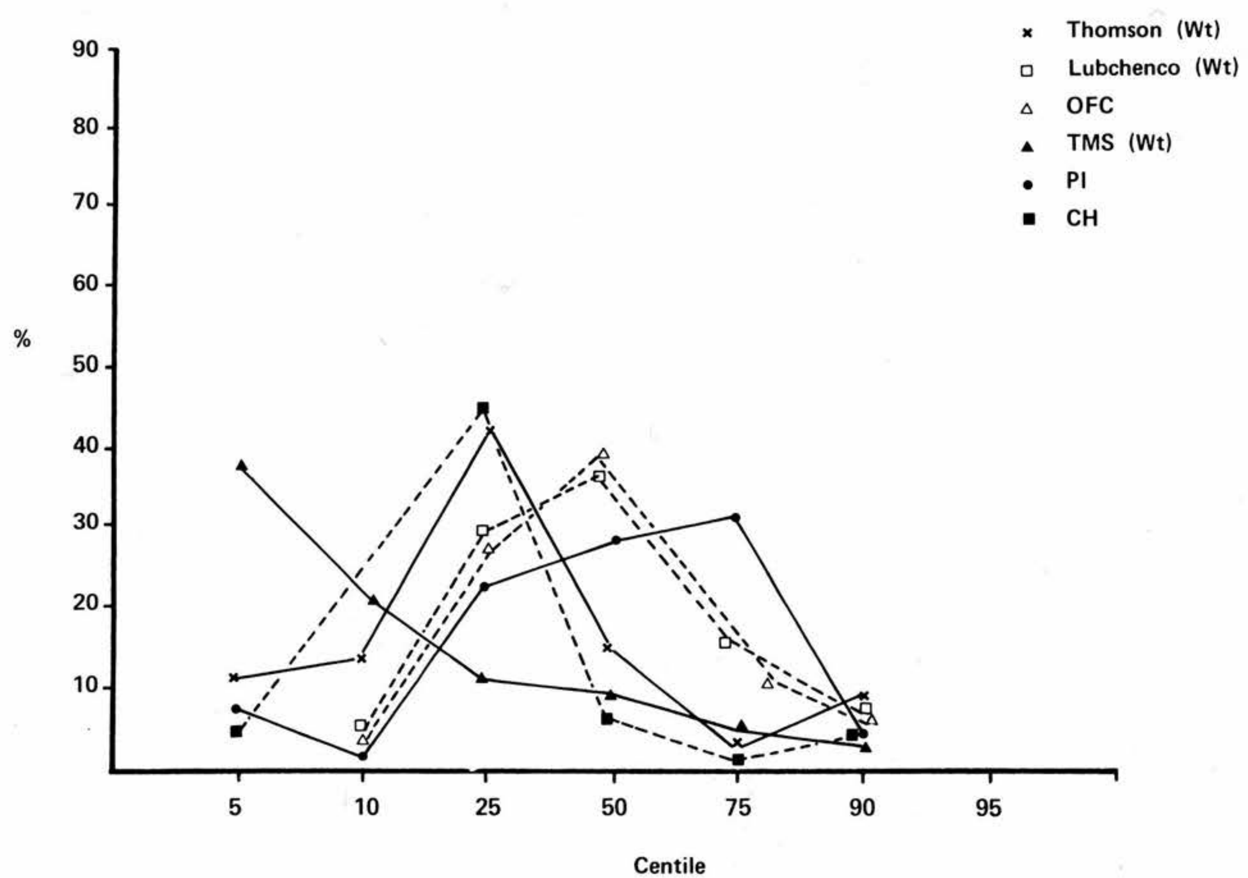
Graph V 2

CENTILE DISTRIBUTION BY SEPARATE DEFINITION
TOTAL LBW



Graph V 3

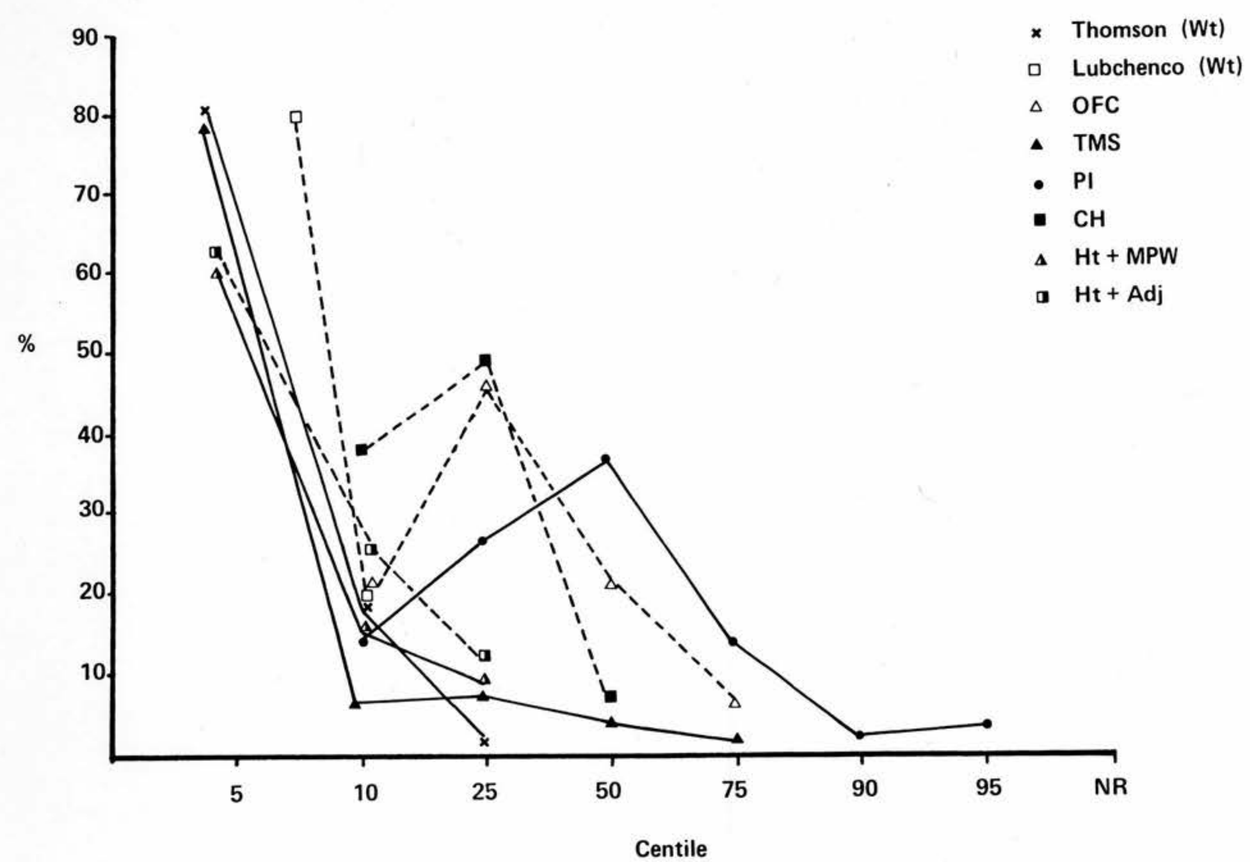
CENTILE DISTRIBUTION BY SEPARATE DEFINITION
LBW 27–36 WEEKS



Graph V 4

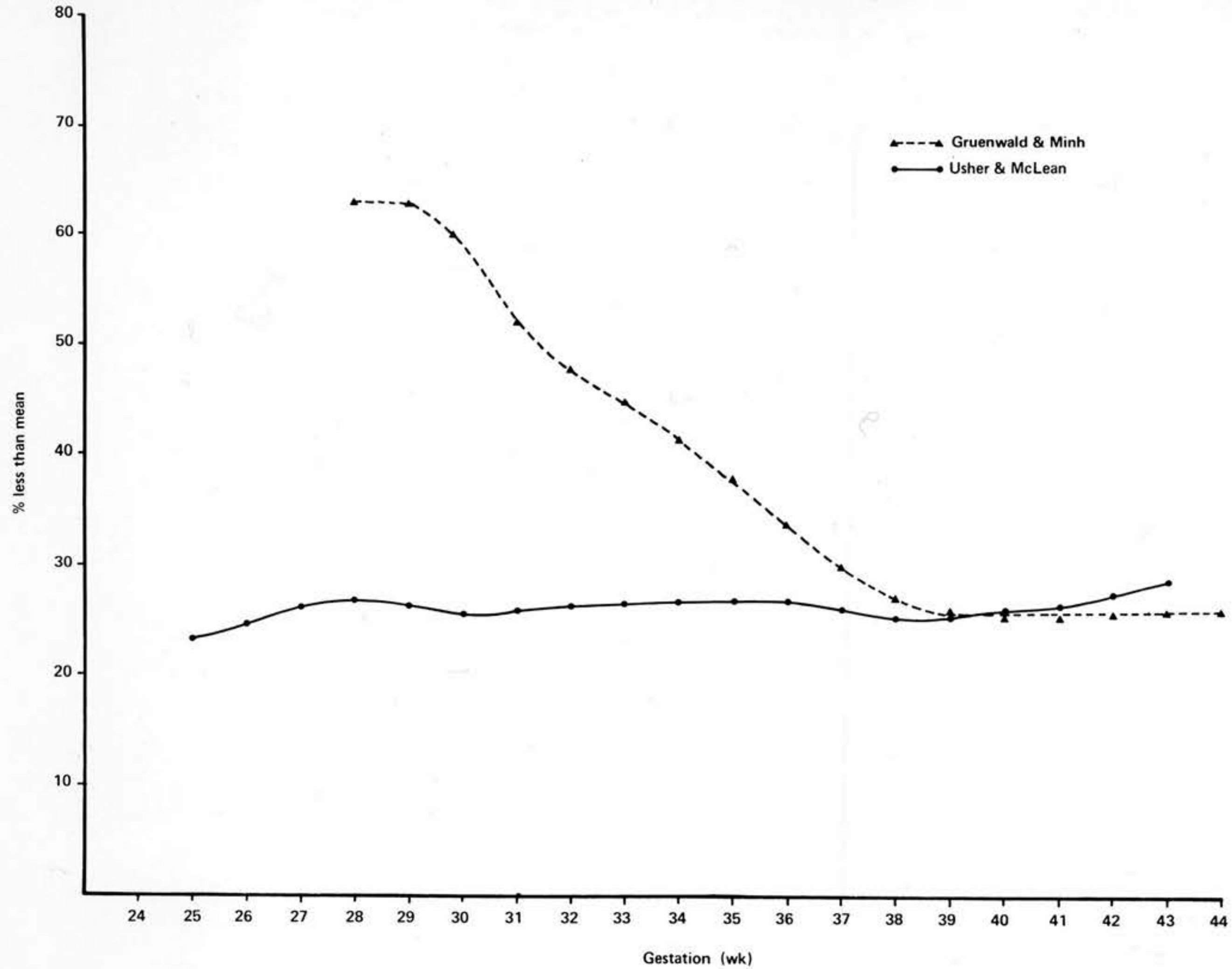
CENTILE DISTRIBUTION BY SEPARATE DEFINITIONS

LBW 37–42 WEEKS



Graph V 5

-2 STANDARD DEVIATION BIRTHWEIGHTS – PERCENTAGE LESS THAN THE MEAN



Graph V 6

10th CENTILE BIRTHWEIGHT – PERCENTAGE LESS THAN THE MEAN

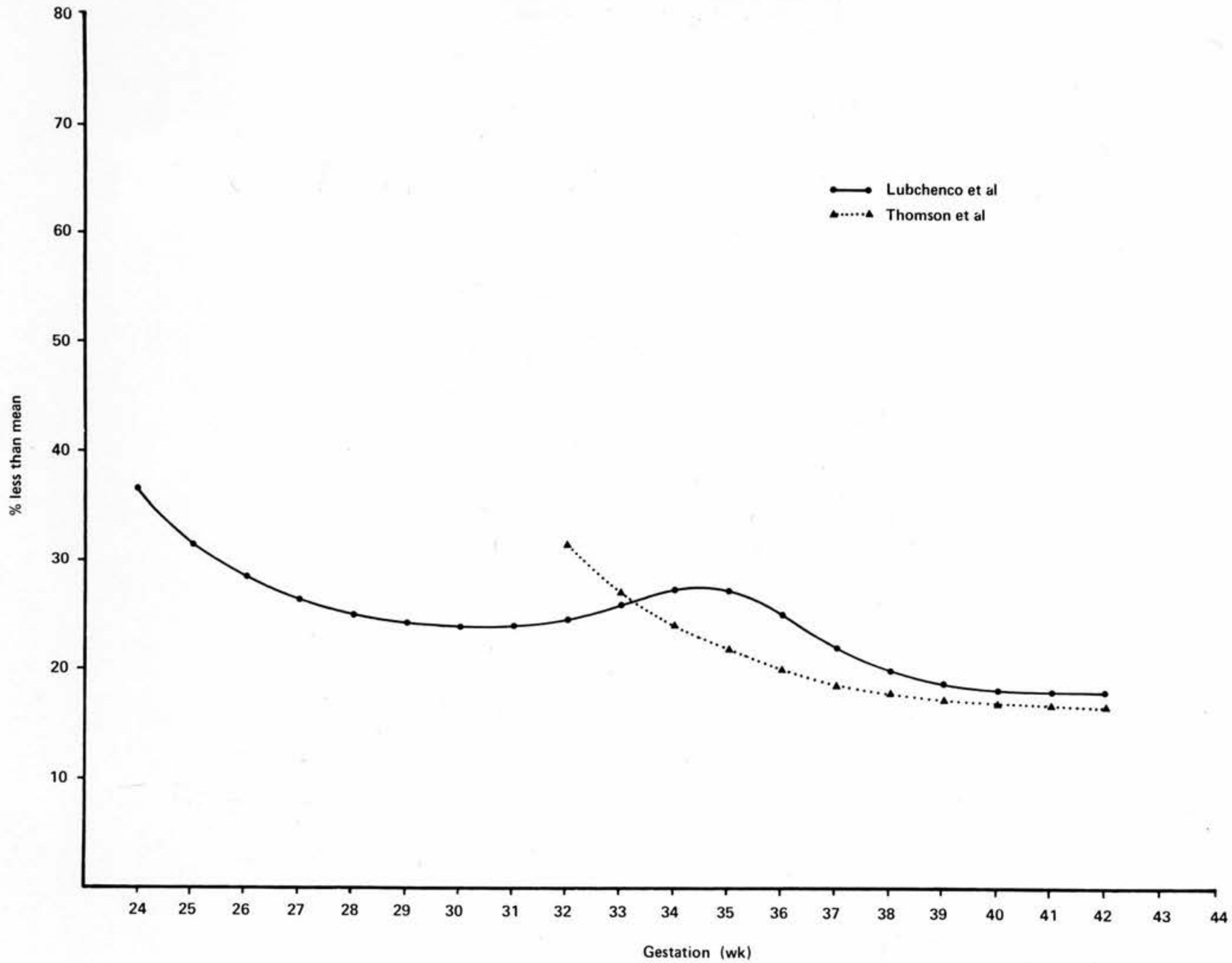


TABLE VI 1

Mothers of Controls - Outcome in other Pregnancies

(adjusted to sex and pregnancy no.)

	Live Births	Normal	Preterm	Preterm IUGR	Term IUGR	Abortion	Uncertain Gestation Category
Previous	116	93	5	5	7	21 (4T)	6 Normal
Subsequent	60	49	2		1	6 (2T)	8 Normal
Total	176	142	7	5	8	27	14 Normal
% Total Pregnancies	86.6	70.0	3.4	2.5	3.9	1.3	6.9

Total Live Births	176
Total Pregnancies	203

T = termination

TABLE VI 2

Mothers of Preterm LBW - Outcome in Other Pregnancies

(adjusted to sex and pregnancy no.)

	Live Births	Normal	Preterm	Preterm IUGR	Term IUGR	Abortion	Uncertain Gestation Category	
Previous	49	35	3	1	6	16 (2T, 1 ectopic)	4	3 LBW 1 Normal
Subsequent	21	12	1		6	4 (1T)	2	1 LBW 1 Normal
Total	70	47	4	1	12	20	6	4 LBW 2 Normal
% Total Pregnancies	77.7	52.2	4.4	1.1	13.3	22.2	6.6	

T = termination

Total Live Births 70

Total Pregnancies 90

TABLE VI 3

Mothers of Preterm IUGR - Outcome in Other Pregnancies

(adjusted to sex and pregnancy no.)

	Live Births	Normal	Preterm	Preterm IUGR	Term IUGR	Abortion	Uncertain Gestation Category	
Previous	28	24			2	7 (1T)	2	1 LBW 1 Normal
Subsequent	5	3		2				
Total	33	27	0	2	2*	7	2	1 LBW 1 Normal
% Total Pregnancies	82.5	67.5	0.0	5.0	5.0	17.5	5.0	

* Still Birth

T = termination

Total Live Births 33

Total pregnancies 40

TABLE VI 4

Mothers of Term IUGR - Outcome in Other Pregnancies

(adjusted to sex and pregnancy no.)

	Live Births	Normal	Preterm	Preterm IUGR	Term IUGR	Abortion	Uncertain Gestation Category	
Previous	59	30	3	2	16	9	8	4 LBW 4 Normal
Subsequent	39	19	4	3	10	5 (1T)	3	0 LBW 3 Normal
Total	98	49	7	5	26	14	11	4 LBW 7 Normal
% Total Pregnancies	87.5	43.7	6.2	4.4	23.2	12.5	9.8	

T = termination

Total Live Births	98
Total Pregnancies	112

TABLE VI 5

Outcome of Pregnancies of Mothers with Repeated LBW Pregnancies

41 Mothers

		%			%
Preterm repeat Preterm	8	19.5	Term repeat Term	9	22.0
Preterm repeat Term	5	12.2	Term repeat Preterm	7	17.0
Preterm repeat Preterm and Term	1	2.4	Term repeat Term and Unknown	1	2.4
Preterm repeat Unknown	5	12.2	Term repeat Preterm and Unknown	1	2.4
			Term repeat Unknown	4	9.8

TABLE VI 6

Theoretical Adjustment of Birth Weight Allowing for Maternal Height in Mothers with Repeated LBW Deliveries

	Controls	Total LBW	Preterm LBW	Term LBW
Mean maternal height adjustment (g)	+ 92.7	+ 94.5	+ 58.1	+ 123.0
S.D. (g)	106.8	140.1	139.7	133.6

TABLE VI 7

Theoretical Adjustment of Birth Weight Allowing for Maternal Height and Midpregnancy Weight in Mothers with Repeated LBW Deliveries

	Controls	Total LBW	Preterm LBW	Term LBW
Mean maternal height and midpregnancy adjustment (g)	+ 48.0	+124.9	+ 79.4	+170.5
S.D. (g)	150.2	182.2	191.4	155.8

TABLE VII 1

Distribution of Control Sample by Gestational Age

Weeks	Certain	Uncertain	Total
34	0	1	1
35	0	0	0
36	0	0	0
37	2	2	4
38	11	9	20
39	20	10	30
40	44	16	60
41	20	9	29
42	1	4	5
Total	98	51	149

TABLE VII 2

Distribution of LBW Sample by Gestational Age

Weeks	Certain	Uncertain	Totals
27	1	1	2
28	2	1	3
29	5	0	5
30	3	0	3
31	1	2	3
32	4	3	7
33	9	3	12
34	6	0	6
35	6	12	18
36	7	7	14
37	9	8	17
38	14	10	24
39	15	8	23
40	5	3	8
41	4	0	4
42	0	0	0
Total	91	58	149

TABLE VII 3

Mean and Standard Deviation of Gestational Age (Completed Weeks) in LBW Infants and Controls According to Degree of Certainty of LMP

	Control	SD	Total LBW	SD	Preterm LBW	SD	Term LBW	SD
Certain	39.7	1.0	35.8	3.5	32.7*	2.6	38.6	1.2
Uncertain	39.5	1.5	36.1	2.8	33.9*	2.3	38.2	1.0
Total	39.7	1.1	35.9	3.2	33.2	2.5	38.4	1.1

* p 0.05

TABLE VII 4

Maternal Disease by Week of Gestation for Control and Term LBW Infants

Groups	Weeks									
	37		38		39		40		41	
	Controls	Term LBW	Controls	Term LBW	Controls	Term LBW	Controls	Term LBW	Controls	Term LBW
Haem. before 28 weeks	0	7	4	4	4	5	9	2	4	1
Other antepartum haemorrhage	0	5	1	2	1	3	2	2	0	0
Other hypertension	0	2	3	3	6	3	7	2	1	1
PET	0	0	1	5	1	0	0	1	0	0
Maternal disease	1	7	6	7	8	9	18	2	11	0
Abortions	0	4	5	8	4	5	10	1	1	0
Total	4	17	20	24	30	23	60	8	29	4

TABLE VII 5

Neonatal Disease by Week of Gestation for Control and term LBW Infants

Groups	37		38		39		40		41	
	Controls	Term LBW	Controls	Term LBW	Controls	Term LBW	Controls	Term LBW	Controls	Term LBW
Cyanotic attacks	0	1	0	5	0	0	1	0	0	0
Silverman score	0	1	0	2	0	1	0	1	0	0
Fetal distress	1	9	7	10	12	11	22	6	9	2
Newborn disease index	0	5	1	7	2	4	3	1	1	0
Total cases	4	17	20	24	30	23	60	8	29	4

TABLE VII 6

Statistical Significance of Differences Between Term LBW and Control Infants for Maternal and Neonatal Disease

37 weeks	
Maternal Disease	$p < 0.005$
38 weeks	
Maternal Disease	$p < 0.05$
Neonatal Disease	$p < 0.001$
Cyanotic Attacks	$p < 0.001$
39 weeks	
Other Hypertension	$p < 0.01$
Maternal Disease	$p < 0.001$
Abortion	$p < 0.025$
40 weeks	
Fetal Distress	$p < 0.025$

(Yates correction for small numbers used throughout this analysis)

TABLE VIII 1

Age at examination for Total Maturity Score

(hours of age)

	Controls	Total LBW
< 12	4	1
12-18	52	46
19-24	41	46
25-30	33	36
31-36	17	13
37-42	0	3
43-48	0	1
49-60	2	0
> 60	0	2
Not examined	0	0
TOTAL	149	149

Controls mean	22.00 hours	S.D	7.47	N.S.
Total LBW mean	23.73 hours	S.D	12.72	
Preterm LBW mean	26.19 hours	S.D	16.37	$p > 0.05$
Term LBW mean	21.40 hours	S.D	7.09	

TABLE VIII 2

Comparison of the mean gestational ages calculated from the Last Menstrual Period and from the Total Maturity Score for mothers with certain dates

	Controls		Total LBW		Preterm BBW		Term LBW	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
G.A. from L.M.P.	40.14	0.99	36.21	3.54	33.14	2.63	39.02	1.16
G.A. from T.M.S.	40.44	0.72	36.88	3.18	34.74	3.01	38.84	1.75
Significance	N.S.		N.S.		$p < 0.02$		N.S.	

TABLE VIII 3

Comparison of the mean gestational ages calculated from the Last Menstrual Period and from the Total Maturity Score for mothers with uncertain dates

	Controls		Total LBW		Preterm LBW		Term LBW	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
G.A. from L.M.P	39.85	1.49	36.47	2.62	34.49	2.29	38.45	0.82
G.A. from T.M.S.	40.09	1.11	37.48	2.58	36.30	2.76	38.70	1.72
Significance	N.S.		$p < 0.05$		$p < 0.01$		N.S.	

TABLE VIII 4

Comparison of the mean gestational ages calculated from the Last Menstrual Period and from the Total Maturity Score for all mothers

	Controls		Total LBW		Preterm LBW		Term LBW	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
G.A. from L.M.P.	40.04	1.19	36.34	3.18	33.69	2.58	38.80	1.08
G.A. from T.M.S.	40.34	0.88	37.11	2.97	35.37	3.01	38.77	1.74
Significance	$p < 0.02$		$p < 0.05$		$p < 0.001$		N.S.	

TABLE VIII 5

Comparison of the difference in weeks between gestational ages derived from the Last Menstrual Period and from the Total Maturity Score

	Controls		Total LBW		Preterm LBW		Term LBW	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Certain	0.28	0.99	0.66	2.10	1.59	2.63	0.17	1.81
Uncertain	0.29	1.62	1.01	2.19	1.82	2.26	0.2	1.79
Significance	N.S.		N.S.		N.S.		N.S.	

TABLE IX 1

Statistical Analysis of the External Characteristics by Controls Infants, Preterm LBW and Term LBW

	Control v Term LBW	Preterm LBW v Term LBW
Skin colour	$p < 0.001$	$p < 0.001$
Skin opacity	$p < 0.001$	$p < 0.001$
Skin texture	$p < 0.005$	$p < 0.001$
Ear form	$p < 0.025$	$p < 0.001$
Ear firmness	$p < 0.001$	$p < 0.001$
Nipple development	$p < 0.001$	$p < 0.001$
Breast size	$p < 0.001$	$p < 0.001$
Plantar skin crease	$p < 0.001$	$p < 0.001$
Oedema	$p < 0.025$	$p < 0.001$
Lanugo hair	NS	$p < 0.001$

TABLE IX 2

Gestation of Groups of Term LBW Infants with either High or Low Score on Selected Items of the TMS

Characteristics	Score	Number	Mean Gestational Age	SD
Skin colour	< 2	12	38.1	0.76
Skin opacity	< 2	27	38.1	0.86
Skin texture	≥ 2	11	39.0*	0.85
Breast size	≥ 2	12	38.9	0.95
Plantar creases	< 2	5	38.8	1.5
Oedema	< 2	10	38.4	1.24
Lanugo hair	< 2	10	38.1	0.94

*$p < 0.05$ (differs significantly from mean gestation of term LBW)

TABLE IX 3

The Effect of Gestational Age on the Sagittal Suture

	Control	Preterm LBW	Term LBW
Separation	81	27	53
Approximated	39	5	6
Overlap	29	39	16
Unrecorded	0	2	1
TOTAL	149	73	76

Preterm LBW - term LBW	$p < 0.001$
Term LBW - controls	$p < 0.005$
Preterm LBW - controls	$p < 0.001$

TABLE IX 4

The Effect of Gestational Age on the Length of Scalp Hair

Length of Hair	Controls	Preterm LBW	Term LBW
1 + cm	99	27	39
- 1 cm	50	40	33
Unrecorded	0	6	4
TOTAL	149	73	76

$p < 0.005$

TABLE IX 5

The Effect of Gestational Age on the Appearance of the Veins in the Cubital Fossa

Appearance	Controls	Preterm LBW	Term LBW
Not visible	124	15	42
Visible	23	54	31
Unrecorded	2	4	3
TOTAL	149	73	76

$p < 0.001$

TABLE IX 6

The Effect of Gestational Age on the Appearance of the Eyelids (Combined)

Appearance	Controls	Preterm LBW	Term LBW
Oedematous	16	25	12
Baggy - Buried	40	21	28
Normal	88	24	36
Unrecorded	5	3	0
TOTAL	149	73	76

$p < 0.001$

TABLE IX 7

The Effects of Gestational Age on Dermal Patterns

Dermal Patterns	Controls	Preterm LBW	Term LBW
+,++,+++ (ve)	54	15	53
+ -	53	12	15
-,--, (ve)	41	43	8
Unrecorded	1	3	0
TOTAL	149	73	76

Preterm LBW v Term LBW	$p < 0.001$
Preterm LBW v Controls	$p < 0.001$
Term LBW v Controls	$p < 0.001$

TABLE IX 8

The Effect of Gestational Age on Condition of Skin on the Hands

Appearance	Controls	Preterm LBW	Term LBW
Cracking/scaling			
peeling	28	4	24
Parchment or Dry	110	17	37
Normal	11	51	13
Unrecorded	0	1	2
TOTAL	149	73	76

Preterm LBW - Term LBW $p < 0.001$

Term LBW - Controls $p < 0.005$

Preterm LBW - Controls $p < 0.001$

TABLE IX 9

The Effect of Gestational Age on the Condition of the Skin

Comparison Between Preterm LBW Term LBW and Control Groups of Infants

Description	Preterm LBW - Term LBW - Controls	Term LBW - Controls
Feet-dorsum	$p < 0.001$	$p < 0.005$
Feet-interdigital	$p < 0.001$	$p < 0.025$
Feet-soles	$p < 0.001$	$p < 0.025$
Hands-dorsum	$p < 0.001$	$p < 0.01$
Hands-interdigital	$p < 0.001$	NS
Hands-palms	$p < 0.001$	NS
Elbows	$p < 0.001$	$p < 0.05$
Ankles	$p < 0.001$	NS

TABLE IX 10

The Effect of Gestation on the Length of First Toe (Right)

Definition	Controls	Preterm LBW	Term LBW
Shorter than second	19	21	17
Equal	39	24	13
Longer than second	88	26	46
Unknown	3	2	0
TOTAL	149	73	76

Preterm LBW - Term LBW	$p < 0.005$
Preterm LBW - Controls	$p < 0.005$
Term LBW - Controls	NS

TABLE IX 11

The Effect of Gestation on Oedema

	Preterm LBW	Term LBW	Significance	Controls	Term LBW	Significance
Circumorbital	21	7	$p < 0.001$	6	7	NS
Tibial	22	14	$p < 0.05$	2	14	*$p < 0.001$
Feet	20	9	$p < 0.01$	1	9	*$p < 0.001$
Hands	13	5	$p < 0.025$	0	5	*$p < 0.025$
Babies with oedema	32	13		4	13	
TOTAL	73	76		149	76	

*with Yates correction

TABLE IX 12

The Effect of IUGR on the Size of the Gastrocnemius Muscle

Description	Controls	Preterm LBW	Term LBW
Small	6	26	27
Moderate or large	142	44	48
Unknown	1	3	1

$p < 0.001$

TABLE IX 13

The Effect of IUGR on Subcutaneous Tibial Loss

Description	Controls	Preterm LBW	Term LBW
+, ++, +++	30	13	45
+ -	60	25	14
-	59	28	17
Unknown	0	7	0
TOTAL	149	73	76

Term LBW v Controls	$p < 0.001$
Preterm LBW v Control	NS

TABLE X 1

Incidence of congenital abnormalities recognised at birth likely to have a significant effect on fetal growth

Condition	Controls	Total LBW	Preterm LBW	Term LBW
Major abnormalities	0	2	1	1
Significant cardiac murmur	-	2	2	0
Hypospadias	3	1	1	0
TOTAL	3	5	4	1

TABLE X 2

Incidence of congenital abnormalities unlikely to have a significant effect on fetal growth

Condition	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW
Congenital dislocation of the hip	4	5	3	1	2
Hernia	0	3	1	0	2
Hydrocele	1	1	0	0	1
Undescended testis	0	4	4	0	0
Cardiac murmur - not significant	2	14	9	1	5
Talipes calcaneovalgus	5	1	1	0	0
Haemangioma	10	14	7	1	7
Sacral sinus	1	2	0	0	2
Single Palmar crease	5	7	3	0	4
TOTAL	28	51	28	3	23

TABLE XI 1

Apgar Scores - 1 Minute

Score	Controls	%	Total LBW	%	Preterm LBW	%	Preterm	%	Term LBW	%
1	1	0.7	6	4.0	4	5.5	1	5.6	2	2.6
2	2	1.3	17	11.4	8	11.0	3	16.7	9	11.8
3	4	2.7	12	8.1	8	11.0	2	11.1	4	5.3
4	7	4.7	8	5.4	6	8.2	1	5.6	2	2.6
5	3	2.0	5	3.4	2	2.7	1	5.6	3	4.0
6	6	4.0	13	8.7	7	9.6	1	5.6	6	7.9
7	5	3.4	14	9.4	6	8.2	1	5.6	8	10.5
8	27	18.1	29	19.5	10	13.7	1	5.6	19	25.0
9	89	59.7	43	28.9	20	27.4	6	33.3	23	30.3
10	5	3.4	0		0		0		0	
Not recorded	0		2	0.7	2	2.7	1	5.6	0	

TABLE XI 2

Apgar Scores at 5 Minutes

Score	Controls	%	Total LBW	%	Preterm LBW	%	Preterm IUGR	%	Term LBW	%
1	0		1	0.7	0		0		1	1.3
2	0		1	0.7	1	1.4	0		0	
3	0		1	0.7	1	1.4	0		0	
4	0		2	1.3	1	1.4	1	5.6	1	1.3
5	1	0.7	4	2.7	3	4.1	2	11.1	1	1.3
6	2	1.3	7	4.7	5	6.9	1	5.6	2	2.6
7	1	0.7	16	10.7	12	16.4	3	16.7	4	5.3
8	9	6.0	26	17.5	15	20.6	3	16.7	11	14.5
9	69	46.3	52	34.9	22	30.1	5	27.8	30	39.5
10	67	45.0	38	25.5	12	16.4	3	16.7	26	34.2
Not recorded	0		1	0.7	1	1.4	0		0	

TABLE XI 3

Apgar Score at 1 Minute

Mean and Standard Deviation

1 Min.

	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW
Mean	8.08	6.41	5.99	5.94	6.78
Standard	1.75	2.72	2.8	3.04	2.62
Totals	149	147	71	16	76

(T-tests)		
	Controls - Total LBW	$p < 0.001$
	Controls - Preterm LBW	$p < 0.001$
	Controls - Preterm IUGR	$p < 0.01$
	Controls - Term LBW	$p < 0.001$
	Preterm LBW - Term LBW	$p < 0.05$

TABLE XI 4

Apgar Score at 5 Minutes

Mean and Standard Deviation

5 Min.

	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW
Mean	9.31	8.29	8.04	7.94	8.79
Standard	0.82	1.9	1.69	1.75	1.52
Totals	149	148	72	17	76

(T-tests)

Controls - Total LBW	$p < 0.001$
Controls - Preterm LBW	$p < 0.002$
Controls - Preterm IUGR	$p < 0.002$
Controls - Term LBW	$p < 0.01$
Total LBW - Term LBW	$p < 0.02$
Preterm LBW - Term LBW	$p < 0.01$

TABLE XI 5

Mode of Delivery

	Controls	Total LBW
Spontaneous vertex	120	90
Caesarean section	10	24
Forceps and other	19	35

$p < 0.001$

	Preterm LBW	Term LBW
Spontaneous vertex	42	48
Caesarean section	14	15
Forceps and other	17	13

NS

	Controls	Total LBW
Spontaneous vertex	120	90
Other	29	59

$p < 0.001$

Difference in no. spontaneous deliveries

Controls v Preterm LBW $p < 0.001$

Controls v Term LBW $p < 0.001$

TABLE XI 6

Mode of Delivery

	Controls	%	Total LBW	%	Preterm LBW	%	Term LBW	%
Spontaneous vertex	120	80.5	90	60.4	42	57.5	48	63.2
Assisted breech	3	2.0	6	4.0	3	4.1	3	3.9
Forceps	15	10.1	29	19.5	14	19.2	15	19.7
Caesarean section	10	6.7	24	16.1	14	19.2	10	13.2
Vacuum extraction	1	0.7	0		0		0	

Controls v Total LBW	$p < 0.001$
Controls v Preterm LBW	$p < 0.001$
Controls v Term LBW	$p < 0.001$
Preterm LBW v Term LBW	NS

TABLE XI 7

Systolic Blood Pressure

(mmHg)

	Controls	%	Total LBW	%	Preterm LBW	%	Term LBW	%
≤30	0		0		0		0	
≤40	0		2	1.3	2	2.7	0	
≤50	0		12	8.1	11	15.1	1	1.3
≤60	11	7.4	52	34.9	29	39.7	23	30.3
≤70	79	53.0	64	42.9	22	30.1	42	55.3
≤80	51	34.2	15	10.1	5	6.9	10	13.2
≤90	5	3.4	0		0		0	
>90	1	0.7	0		0		0	
Not recorded	2	1.3	4	2.7	4	5.5	0	
Total	149		149		73		76	

TABLE XI 8

Blood Pressure

	Controls	Total LBW	Preterm LBW	Term LBW
BP mmHg	69.1	60.6	58.0	63.7
SD	6.2	8.9	8.2	6.0

Significance	Controls v Total LBW	$p < 0.001$
	Controls v Term LBW	$p < 0.001$
	Controls v Preterm LBW	$p < 0.001$
	Preterm LBW v Term LBW	$p < 0.001$

TABLE XI 9

Blood Glucose in Relation to Age

(correlation coefficient)

Hours of Age	Controls	Total LBW	Preterm LBW	Term LBW
1 - 10	+ 0.07	+ 0.38	+ 0.43	+ 0.37
11 - 20	+ 0.24	- 0.04	+ 0.32	+ 0.07
21 - 30	+ 0.17	- 0.15	- 0.04	- 0.18
31 - 40	+ 0.05	- 0.01	+ 0.12	+ 0.04
41 - 50	+ 0.07	- 0.01	- 0.22	- 0.05
51 - 60	- 0.06	0.0	- 0.01	+ 0.05
61 - 70	+ 0.11	+ 0.17	+ 0.29	+ 0.17
Total	+ 0.28	+ 0.22	+ 0.32	+ 0.19

TABLE XII 1

CNS Disorders

	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW	<1500 g
Delayed Development	0	9	7	4	2*	4
Cerebral Palsy	0	3	2	1	1	0
Convulsion (Febrile)	0	9	6(3)	1(1)	3(1)	1
Hydrocephalus	0	1	0	0	1	0
Strabismus	2	6	4	2	2	0

*(1 case Epiloia. 1 case Taybi-Rubenstein)

TABLE XII 2

Gastrointestinal Disorders

	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW	<1500 g
Inguinal Hernia	1	6	4	1	2	0
Umbilical Hernia	0	3	0	0	3	0
Hiatus Hernia	1*	0	0	0	0	0
Diarrhoea and Vomiting	9(4)	16(7)	7(3)	3	9(4)	2(1)

*(with pyloric stenosis)

TABLE XII 3

Ear, Nose and Throat Conditions

	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW	<1500 g
Otitis Media	6	5	4	2	1	1
Tonsillectomy and Adenoidectomy	0	12	3	1	9	0
Tonsillectomy	1	2	1	0	1	0

TABLE XII 4

Social Problems and Psychiatric Problems

	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW	<1500 g
Ingestion of poisonous substance	2	6	3	0	3	1
Social problem	2	4	2	0	2	1
Behaviour disorder	2	1	0	0	1	0
Psychiatric problem	1	3	1	0	2	1
Enuresis	0	3	0	0	3	0

TABLE XII 5

Trauma

	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW	<1500 g
Fractures -						
Long bones	3	4	3	2	1	0
Small bones/greenstick	1	3	3	0	0	0
Falls	0	3	2	1	0	0
Scald/burn	0	5	4	0	1	0
Head injury	4	4	3	0	1	2
Non-accidental	1	4	3	0	1	0
Foreign Body	0	2	1	0	1	1
Amputation	1	0	0	0	0	0

TABLE XII 6

Skin Disorders

	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW	< 1500 g
Napkin rash	0	4	2	0	2	1
Eczema	4	3	1	0	2	0
Scabies	2	4	3	0	1	0
Seborrhoeic Dermatitis	0	1	1	0	0	1

TABLE XII 7

Orthopaedic Conditions

		Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW	< 1500 g
Congenital dislocation of hip		13	33	19	7	14	4
Talipes	TEV	0	1	1	0	0	0
	TCV	4	0	0	0	0	0

TABLE XII 8

Miscellaneous Conditions

	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW	<1500 g
Anaemia	1	11	8	1	3	0
Blindness	0	1	0	0	1	1
Hypermetropia	1	0	0	0	0	0
Blocked Lachrymal Duct	4	2	0	0	2	0
Deafness (Congenital)	1	0	0	0	0	0
Miscellaneous Eye Conditions	2	1	0	0	1	0
Nephrotic Syndrome	0	1	1	1	0	0
Haemolytic-uraemic Syndrome	1	0	0	0	0	0
Urinary Infection	2	3	2	0	1	0
Congenital Laryngeal Stridor	1	1	1	0	0	0
Haemangioma	3	2	1	0	1	0
Hamartoma	1	0	0	0	0	0
Coccygeal Sinus	0	1	0	0	1	0
Perthes Disease	2	0	0	0	0	0
Rheumatoid Arthritis	0	1	0	0	1	0
Painful Joints	0	2	1	0	1	0
Phimosis	2	1	1	0	0	0
Hypospadias	2	1	1	0	0	0
Intersex (Female mosaic)	0	1	1	0	0	0
Breast Hypertrophy (Unilateral	1	0	0	0	0	0
Heart Murmur	0	2	2	0	0	0
Abscess	0	1	1	0	0	0
Bat Ears	0	1	0	0	1	0
Rubella Syndrome	0	1	0	0	1	0
Dental Extraction	2	2	0	0	2	0
Pyrexia of unknown origin	0	1	1	0	0	0
Death - Gauchers Disease	0	1	0	0	1	0
	26	38	21	2	17	1

TABLE XII 9

Casualty Attendance

	Controls	Total LBW	Preterm LBW	Preterm IUGR	Term LBW	< 1500 g
No. of attendances in each group (not mutually exclusive)	(145)	(159)	(81)	(20)	(78)	(9)
Miscellaneous	75	77	39	7	38	4
Head Injury	43	48	23	9	25	1
Other Falls	5	4	2	0	2	2
Ingestion of noxious substance	5	12	6	1	6	1
Fractures	5	2	2	0	0	0
Scalds	8	11	6	3	5	1
Burns	4	5	3	0	2	0

TABLE XII 10

Casualty Visits (Total Number) by Sex

	Controls	LBW
Males	98	87
Females	51	81

Significance $p < 0.05$

TABLE XII 11

Children with four or more Casualty Visits

	Controls	LBW
Males	5	6
Females	1	13
Total	6	19

Significance $p < 0.01$

with Yates correction

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